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(54) Title: ARYLOXYALKYLAMINE DERIVATES AS H3 RECEPTOR LIGANDS

(57) Abstract: The present invention relates to novel benzyloxy derivatives having pharmacological activity, processes for their preparation, to compositions containing them and to their use in the treatment of neurological and psychiatric disorders.

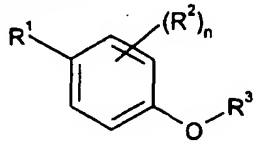
ARYLOXYALKYLAMINE DERIVATIVES AS H3 RECEPTOR LIGANDS

The present invention relates to novel phenoxy derivatives having pharmacological activity, processes for their preparation, to compositions containing them and to their use in the treatment of neurological and psychiatric disorders.

WO 02/76925 (Eli Lilly), WO 00/06254 (Societe Civile Bioprojet), WO 01/66534 (Abbott Laboratories) and (WO 03/004480 (Novo Nordisk) describe a series of compounds which are claimed to be histamine H3 antagonists. WO 02/40466 (Ortho McNeill Pharmaceutical) disclose a series of amido-alkyl piperidine and amido-alkyl piperazine derivatives which are claimed to be useful in treatment of various nervous system disorders.

The histamine H3 receptor is predominantly expressed in the mammalian central nervous system (CNS), with minimal expression in peripheral tissues except on some sympathetic nerves (Leurs *et al.*, (1998), Trends Pharmacol. Sci. **19**, 177-183). Activation of H3 receptors by selective agonists or histamine results in the inhibition of neurotransmitter release from a variety of different nerve populations, including histaminergic and cholinergic neurons (Schlicker *et al.*, (1994), Fundam. Clin. Pharmacol. **8**, 128-137). Additionally, *in vitro* and *in vivo* studies have shown that H3 antagonists can facilitate neurotransmitter release in brain areas such as the cerebral cortex and hippocampus, relevant to cognition (Onodera *et al.*, (1998), In: The Histamine H3 receptor, ed Leurs and Timmerman, pp255-267, Elsevier Science B.V.). Moreover, a number of reports in the literature have demonstrated the cognitive enhancing properties of H3 antagonists (e.g. thioperamide, clobenpropit, ciproxifan and GT-2331) in rodent models including the five choice task, object recognition, elevated plus maze, acquisition of novel task and passive avoidance (Giovanni *et al.*, (1999), Behav. Brain Res. **104**, 147-155). These data suggest that novel H3 antagonists and/or inverse agonists such as the current series could be useful for the treatment of cognitive impairments in neurological diseases such as Alzheimer's disease and related neurodegenerative disorders.

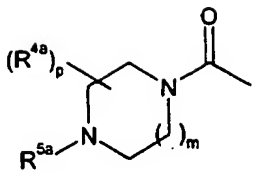
The present invention provides, in a first aspect, a compound of formula (I) or a pharmaceutically acceptable salt thereof:



(I)

wherein:

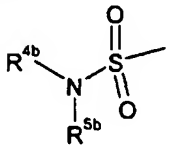
R^1 represents a group of formula (A):



(A)

wherein R^{4a} represents C_{1-6} alkyl, oxo, aryl, heteroaryl or heterocyclyl;
R^{5a} represents hydrogen, -C_{1-6} alkyl, -C_{1-6} alkylC_{1-6} alkoxy, -C_{1-6} alkoxycarbonyl, -C_{3-8} cycloalkyl, -aryl, -heterocyclyl, heteroaryl, -C_{1-6} alkyl-aryl, -CH(aryl)(aryl), -C_{1-6} alkyl-C_{3-8} cycloalkyl, -C_{1-6} alkyl-heteroaryl or -C_{1-6} alkyl-heterocyclyl,
wherein R^{5a} may be optionally substituted by one or more (eg. 1, 2 or 3) substituents which may be the same or different, and which are selected from the group consisting of halogen, hydroxy, cyano, nitro, oxo, haloC_{1-6} alkyl, polyhaloC_{1-6} alkyl, haloC_{1-6} alkoxy, polyhaloC_{1-6} alkoxy, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} alkylthio, C_{1-6} alkoxyC_{1-6} alkyl, C_{3-7} cycloalkylC_{1-6} alkoxy, C_{1-6} alkanoyl, C_{1-6} alkoxycarbonyl, C_{1-6} alkylsulfonyl, C_{1-6} alkylsulfinyl, C_{1-6} alkylsulfonyloxy, C_{1-6} alkylsulfonylC_{1-6} alkyl, C_{1-6} alkylsulfonamidoC_{1-6} alkyl, C_{1-6} alkylamidoC_{1-6} alkyl or a group $NR^{15a}R^{16a}$, -$CONR^{15a}R^{16a}$, -$NR^{15a}COR^{16a}$, -$NR^{15a}SO_2R^{16a}$ or -$SO_2NR^{15a}R^{16a}$, wherein R^{15a} and R^{16a} independently represent hydrogen, C_{1-6} alkyl, aryl or together with the nitrogen to which they are attached may form a nitrogen containing heterocyclyl group;;
m is 1 or 2;
p is 0, 1, 2 or 3, or when p represents 2, said R^{4a} groups may instead form a bridging group consisting of one or two methylene groups;

or R^1 represents a group of formula (B):

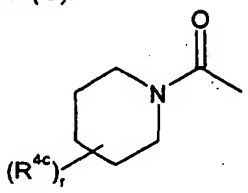


(B)

wherein $NR^{4b}R^{5b}$ represents an N-linked –heterocyclyl, -heterocyclyl-X^b-aryl, -heterocyclyl-X^b-heteroaryl, –heterocyclyl–X^b-heterocyclyl, -heteroaryl, -heteroaryl-X^b-aryl, -heteroaryl-X^b-heteroaryl or –heteroaryl-X^b-heterocyclyl group;
wherein said aryl, heteroaryl and heterocyclyl groups of $NR^{4b}R^{5b}$ may be optionally substituted by one or more (eg. 1, 2 or 3) substituents which may be the same or different, and which are selected from the group consisting of halogen, hydroxy, cyano, nitro, oxo, haloC_{1-6} alkyl, polyhaloC_{1-6} alkyl, haloC_{1-6} alkoxy, polyhaloC_{1-6} alkoxy, C_{1-6} alkyl, C_{1-6} alkoxy, arylC_{1-6} alkoxy, C_{1-6} alkylthio, C_{1-6} alkoxyC_{1-6} alkyl, C_{3-7} cycloalkylC_{1-6} alkoxy, C_{1-6} alkanoyl, C_{1-6} alkoxycarbonyl, arylC_{1-6} alkyl, heteroarylC_{1-6} alkyl, C_{1-6} alkylsulfonyl, C_{1-6} alkylsulfinyl, C_{1-6} alkylsulfonyloxy, C_{1-6} alkylsulfonylC_{1-6} alkyl, arylsulfonyl, arylsulfonyloxy, arylsulfonylC_{1-6} alkyl, aryloxy, C_{1-6} alkylsulfonamidoC_{1-6} alkyl, C_{1-6} alkylamidoC_{1-6} alkyl, arylsulfonamido, arylaminosulfonyl, arylsulfonamidoC_{1-6} alkyl, arylcarboxamidoC_{1-6} alkyl, aroylC_{1-6} alkyl, arylC_{1-6} alkanoyl, or a group -$NR^{15b}R^{16b}$, -

$CONR^{15b}R^{16b}$, $-NR^{15b}COR^{16b}$, $-NR^{15b}SO_2R^{16b}$ or $-SO_2NR^{15b}R^{16b}$, wherein R^{15b} and R^{16b} independently represent hydrogen or C_{1-6} alkyl;
X^b represents a bond, CO, NHCO or CONH;

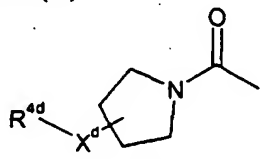
or R^1 represents a group of formula (C):



(C)

wherein R^{4c} represents C_{1-6} alkyl, OH, aryl or heterocyclyl, wherein said aryl and heterocyclyl groups may be optionally substituted by halogen, C_{1-6} alkyl, C_{1-6} alkoxy, cyano, amino, oxo, trifluoromethyl or an aryl group;
r is 0, 1 or 2;

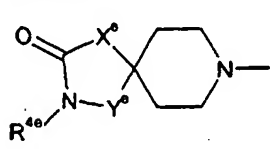
or R^1 represents a group of formula (D):



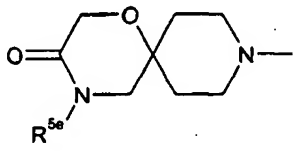
(D)

wherein R^{4d} represents aryl or heteroaryl wherein said aryl and heteroaryl groups may be optionally substituted by one or more (eg. 1, 2 or 3) substituents which may be the same or different, and which are selected from the group consisting of halogen, C_{1-6} alkyl, C_{1-6} alkoxy, cyano, amino or trifluoromethyl;
X^d represents a bond or NHCO, such that when X^d represents NHCO, the group R^{4d}-X^d is attached at the 3-position of the pyrrolidinyl ring;

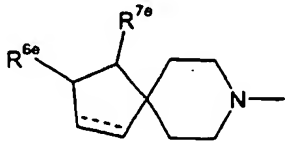
or R^1 represents a group of formula –CO-E, wherein E represents a group of formula E^a, E^b or E^c:



(E^a)



(E^b)



(E^c)

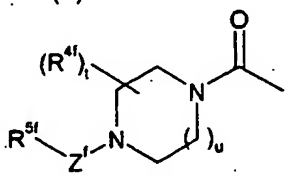
wherein X^e represents O or N-R^{8e};
Y^e represents –C(HR^{9e})- or –C(=O)-;
R^{4e}, R^{5e}, R^{8e} and R^{9e} independently represent hydrogen, C_{1-6} alkyl, aryl, heteroaryl, -C_{1-6} alkyl-aryl or -C_{1-6} alkyl-heteroaryl;

R^{6e} and R^{7e} independently represent hydrogen, C_{1-6} alkyl, aryl, heteroaryl, -C_{1-6} alkyl-aryl, -C_{1-6} alkyl-heteroaryl or R^{6e} and R^{7e} together with the carbon atoms to which they are attached may form a benzene ring;

------ is a single or double bond;

wherein said aryl or heteroaryl groups of R^{4e}, R^{5e}, R^{6e}, R^{7e}, R^{8e} and R^{9e} may be optionally substituted by one or more (eg. 1, 2 or 3) substituents which may be the same or different, and which are selected from the group consisting of C_{1-6} alkyl, CF_3, C_{1-6} alkoxy, halogen, cyano, sulfonamide or C_{1-6} alkylsulfonyl;

or R^1 represents a group of formula (F):



(F)

wherein t is 0, 1 or 2;

u is 1 or 2;

R^{4f} represents C_{1-6} alkyl or when t represents 2, said R^{4f} groups may instead form a bridging group consisting of one or two methylene groups;

R^{5f} represents -C_{1-6} alkyl, -C_{1-6} alkylC_{1-6} alkoxy, -C_{3-8} cycloalkyl, aryl, heterocyclyl, heteroaryl, -C_{1-6} alkyl-aryl, -C_{1-6} alkyl-C_{3-8} cycloalkyl, -C_{1-6} alkyl-heteroaryl, -C_{1-6} alkyl-heterocyclyl, -aryl-aryl, -aryl-heteroaryl, -aryl-heterocyclyl, -heteroaryl-aryl, -heteroaryl-heteroaryl, -heteroaryl-heterocyclyl, -heterocyclyl-aryl, -heterocyclyl-heteroaryl or -heterocyclyl-heterocyclyl;

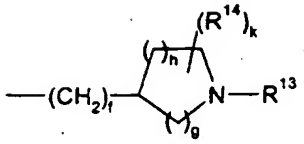
wherein R^{5f} may be optionally substituted by one or more (eg. 1, 2 or 3) substituents which may be the same or different, and which are selected from the group consisting of halogen, hydroxy, cyano, nitro, oxo, haloC_{1-6} alkyl, polyhaloC_{1-6} alkyl, haloC_{1-6} alkoxy, polyhaloC_{1-6} alkoxy, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} alkylthio, C_{1-6} alkoxyC_{1-6} alkyl, C_{3-7} cycloalkylC_{1-6} alkoxy, C_{1-6} alkanoyl, C_{1-6} alkoxycarbonyl, C_{1-6} alkylsulfonyl, C_{1-6} alkylsulfinyl, C_{1-6} alkylsulfonyloxy, C_{1-6} alkylsulfonylC_{1-6} alkyl, C_{1-6} alkylsulfonamidoC_{1-6} alkyl, C_{1-6} alkylamidoC_{1-6} alkyl, arylsulfonyl, arylsulfonyloxy, aryloxy, arylsulfonamido, arylcarboxamido, aroyl, or a group $NR^{15f}R^{16f}$, -$CONR^{15f}R^{16f}$, -$NR^{15f}COR^{16f}$, -$NR^{15f}SO_2R^{16f}$ or -$SO_2NR^{15f}R^{16f}$, wherein R^{15f} and R^{16f} independently represent hydrogen or C_{1-6} alkyl or together form a heterocyclic ring;

Z^f represents CO or SO_2;

R^2 represents halogen, C_{1-6} alkyl, C_{1-6} alkoxy, cyano, amino or trifluoromethyl;

n is 0, 1 or 2;

R^3 represents -$(CH_2)_q$-$NR^{11}R^{12}$ or a group of formula (i):



(i)

wherein q is 2, 3 or 4;
R^{11} and R^{12} independently represent C_{1-6} alkyl or together with the nitrogen atom to which they are attached represent an N-linked heterocyclic group selected from pyrrolidine, piperidine and homopiperidine optionally substituted by one or two R^{17} groups;
R^{13} represents C_{1-6} alkyl, C_{3-6} cycloalkyl or -C_{1-4} alkyl-C_{3-6} cycloalkyl;
R^{14} and R^{17} independently represent halogen, C_{1-6} alkyl, haloC_{1-6} alkyl, OH, diC_{1-6} alkylamino or C_{1-6} alkoxy;
f and k independently represent 0, 1 or 2;
g is 0, 1 or 2 and h is 0, 1, 2 or 3, such that g and h cannot both be 0;
or solvates thereof.

In one particular aspect of the present invention, when R^1 represents a group of formula (F), R^{5f} is linked to Z^f via a carbon atom, u represents 1 and Z^f represents CO.

Alkyl groups, whether alone or as part of another group, may be straight chain or branched and the groups alkoxy and alkanoyl shall be interpreted similarly. Alkyl moieties are more preferably C_{1-4} alkyl, eg. methyl or ethyl. The term 'halogen' is used herein to describe, unless otherwise stated, a group selected from fluorine, chlorine, bromine or iodine.

The term "aryl" includes single and fused rings wherein at least one ring is aromatic, for example, phenyl, naphthyl and tetrahydronaphthalenyl.

The term "heterocyclyl" is intended to mean a 4-7 membered monocyclic saturated or partially unsaturated aliphatic ring or a 4-7 membered monocyclic saturated or partially unsaturated aliphatic ring fused to a benzene ring containing 1 to 3 heteroatoms selected from oxygen or nitrogen. Suitable examples of such monocyclic rings include pyrrolidinyl, piperidinyl, piperazinyl, morpholinyl, diazepanyl, azepanyl, dihydroimidazolyl, tetrahydropyranyl and tetrahydrofuranyl. Suitable examples of benzofused heterocyclic rings include indolinyl, isoindolinyl and tetrahydroisoquinolinyl.

The term "nitrogen containing heterocyclyl" is intended to represent any heterocyclyl group as defined above which contains a nitrogen atom.

The term "heteroaryl" is intended to mean a 5-7 membered monocyclic aromatic or a fused 8-11 membered bicyclic aromatic ring containing 1 to 3 heteroatoms selected from

oxygen, nitrogen and sulphur. Suitable examples of such monocyclic aromatic rings include thienyl, furyl, pyrrolyl, triazolyl, imidazolyl, oxazolyl, thiazolyl, oxadiazolyl, isothiazolyl, isoxazolyl, thiadiazolyl, pyrazolyl, pyrimidyl, pyridazinyl, pyrazinyl and pyridyl. Suitable examples of such fused aromatic rings include benzofused aromatic rings such as quinolinyl, isoquinolinyl, quinazolinyl, quinoxalinyl, cinnolinyl, naphthyridinyl, indolyl, indazolyl, pyrrolopyridinyl, benzofuranyl, benzothienyl, benzimidazolyl, benzoxazolyl, benzisoxazolyl, benzothiazolyl, benzisothiazolyl, benzoxadiazolyl, benzothiadiazolyl and the like.

Preferably, n represents 0.
Preferably, R^3 represents $-(CH_2)_q-NR^{11}R^{12}$.
Preferably, q is 3.
Preferably, $NR^{11}R^{12}$ represents an N-linked heterocyclic group, more preferably unsubstituted piperidine.

For compounds of formula (I) wherein R^1 represents a group of formula (A):
Preferably, R^{5a} represents:

hydrogen;

C_{1-6} alkyl (eg. methyl or i-propyl) optionally substituted by $-CONR^{15a}R^{16a}$ (eg. $CONMe_2$, CONMe-phenyl, CO-N-piperidine or CO-N-pyrrolidine);

C_{1-6} alkoxycarbonyl (eg. t-butoxycarbonyl);

-aryl (eg. phenyl) optionally substituted by one or more (eg. 1, 2 or 3) cyano, halogen (eg. fluorine or chlorine), C_{1-6} alkyl (eg. methyl), C_{1-6} alkoxy (eg. methoxy), polyhaloC_{1-6} alkyl (eg. trifluoromethyl) or C_{1-6} alkanoyl (eg. $COCH_3$) groups;

heteroaryl (eg. pyridyl, pyrimidyl, pyridazinyl, pyrazinyl, quinolinyl or benzothiazolyl) optionally substituted by one or more (eg. 1, 2 or 3) oxo, cyano, halogen (eg. chlorine), C_{1-6} alkyl (eg. methyl) or polyhaloC_{1-6} alkyl (eg. trifluoromethyl) groups;

$-C_{1-6}$ alkyl-heterocyclyl (eg. $-CH_2$-tetrahydrofuranyl);

$-C_{3-8}$ cycloalkyl (eg. cycloheptyl);

$-C_{1-6}$ alkyl-heteroaryl (eg. $-CH_2$-pyridyl);

-heteroaryl-aryl (eg. –thiadiazolyl-phenyl); or

-CH(aryl)(aryl) (eg. –CH(phenyl)(phenyl)).

Preferably, m represents 1.
When n represents 1, R^2 is preferably halogen (eg. fluorine) or trifluoromethyl. When n represents 2, R^2 is preferably halogen (eg. fluorine).
Preferably, p represents 0, 1 or 2, more preferably 0.
When p represents 1, preferably R^{4a} represents oxo or C_{1-6} alkyl (eg. methyl).
When p represents 2, preferably R^{4a} represents C_{1-6} alkyl (eg. methyl) or forms a methylene bridging group.

For compounds of formula (I) wherein R^1 represents a group of formula (B):

Preferably, $NR^{4b}R^{5b}$ represents an N-linked heterocyclyl (eg. morpholinyl, piperidinyl, indolinyl, isoindolinyl or piperazinyl) or a -heterocyclyl-X^b-aryl group (eg. -piperidinyl-phenyl, -piperazinyl-phenyl, -piperazinyl-CO-phenyl or –piperazinyl-CO-naphthyl) optionally substituted by a polyhaloC_{1-6} alkoxy (eg. trifluoromethoxy) group.

For compounds of formula (I) wherein R^1 represents a group of formula (C):
When present, R^{4c} preferably represents aryl (eg. phenyl), C_{1-6} alkyl (eg. methyl), OH or an optionally substituted heteroaryl group (eg. dihydroimidazol-2-one substituted by phenyl), more preferably R^{4c} represents methyl.
When n represents 1, R^2 is preferably halogen (eg. fluorine) or trifluoromethyl. When n represents 2, R^2 is preferably halogen (eg. fluorine).
When r represents 2, preferably R^{4c} represents methyl.

For compounds of formula (I) wherein R^1 represents a group of formula (D):
Preferably, R^{4d} represents phenyl or naphthyl, more preferably unsubstituted phenyl or naphthyl.

For compounds of formula (I) wherein R^1 represents a group of formula (E^a):
X^e is preferably O or NH, R^{4e} is preferably aryl (eg. phenyl) or -C_{1-6} alkyl-aryl (eg. benzyl) and Y^e is preferably $–CH_2–$.

For compounds of formula (I) wherein R^1 represents a group of formula (E^b):
R^{5e} is preferably aryl (eg. phenyl).

For compounds of formula (I) wherein R^1 represents a group of formula (E^c):
R^{6e} and R^{7e}, together with the carbon atoms to which they are attached preferably form a benzene ring and ------ is preferably a double bond.

For compounds of formula (I) wherein R^1 represents a group of formula (F):
Preferably, R^{5f} represents:

-C_{1-6} alkyl (eg. i-propyl);

-C_{3-8} cycloalkyl (eg. cyclohexyl or cycloheptyl);

aryl (eg. phenyl or tetrahydronaphthalene) optionally substituted by a halogen atom (eg. chlorine), cyano, N-propyl$_2SO_2$- or a polyhaloC_{1-6} alkyl group (eg. trifluoromethyl);

-heteroaryl (eg. furyl, thienyl, pyridyl, quinoxaline, pyrazine, 1,2,3-benzothiadiazole, benzofuranyl, isoxazole or pyrazole) optionally substituted by a halogen atom (eg. chlorine), polyhaloC_{1-6} alkyl group (eg. trifluoromethyl) or C_{1-6} alkyl (eg. methyl or t-butyl);

-heterocyclyl (eg. morpholine, pyrrolidine, tetrahydrofuran or tetrahydropyran);

-C_{1-6} alkyl-aryl (eg. α-methylbenzyl or α,α-dimethylbenzyl).

Preferably, R^{5f} is optionally substituted by one or more (eg. 1, 2 or 3) halogen (eg. chlorine), cyano, trifluoromethyl, C_{1-6} alkyl (eg. methyl or t-butyl), $MeSO_2$- or N-propyl$_2SO_2$- groups.

More preferably, R^{5f} represents C_{3-8} cycloalkyl (eg. cyclohexyl), heteroaryl (eg. furyl) or aryl (eg. phenyl or tetrahydronaphthalene) optionally substituted by a cyano group.

Preferably, Z^f represents CO.

When n represents 1, R^2 is preferably trifluoromethyl.

Preferably, t represents 0 or 2, more preferably 0.

When t represents 2, both R^{4f} groups are preferably methyl or form a methylene bridging group.

Preferably, u represents 1.

When R^3 represents a group of formula (i), preferably f represents 0, h represents 1, g represents 2, k represents 0 and R^{13} represents C_{1-6} alkyl (eg. isopropyl) or C_{3-6} cycloalkyl (eg. cyclobutyl or cyclopentyl).

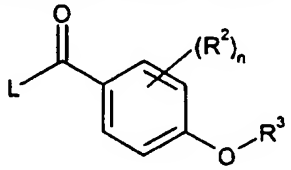
Preferred compounds according to the invention include examples E1-E172 as shown below, or a pharmaceutically acceptable salt thereof.

Compounds of formula (I) may form acid addition salts with acids, such as conventional pharmaceutically acceptable acids, for example maleic, hydrochloric, hydrobromic, phosphoric, acetic, fumaric, salicylic, sulphate, citric, lactic, mandelic, tartaric and methanesulphonic. Salts, solvates and hydrates of histamine H3 receptor antagonists therefore form an aspect of the invention.

Certain compounds of formula (I) are capable of existing in stereoisomeric forms. It will be understood that the invention encompasses all geometric and optical isomers of these compounds and the mixtures thereof including racemates. Tautomers also form an aspect of the invention.

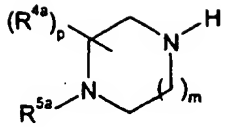
The present invention also provides a process for the preparation of a compound of formula (I) or a pharmaceutically acceptable salt thereof, which process comprises:

(a) preparing a compound of formula (I) wherein R^1 represents a group of formula (A) which comprises reacting a compound of formula (II)



(II)

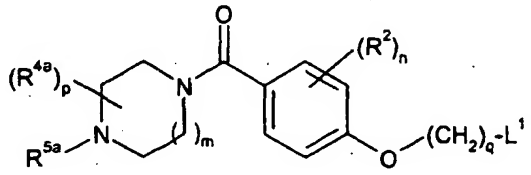
with a compound of formula (III)



(III)

or a protected derivative thereof, wherein R^2, R^3, R^{4a}, R^{5a}, m, n and p are as defined above and L is OH or a suitable leaving group (eg. a halogen atom such as chlorine); or

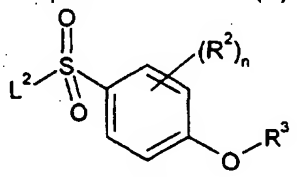
(b) preparing a compound of formula (I) wherein R^1 represents a group of formula (A) and wherein R^3 represents $-(CH_2)_q-NR^{11}R^{12}$ which comprises reacting a compound of formula (IV)



(IV)

wherein R^2, R^{4a}, R^{5a}, m, n, p and q are as defined above and L^1 represents a suitable leaving group such as a halogen atom (eg. bromine) with a compound of formula $HNR^{11}R^{12}$; wherein R^{11} and R^{12} are as defined above; or

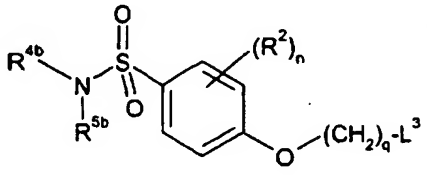
(c) preparing a compound of formula (I) wherein R^1 represents a group of formula (B) which comprises reacting a compound of formula (V)



(V)

with a compound of formula $R^{4b}R^{5b}NH$ wherein R^2, R^3, R^{4b}, R^{5b} and n are as defined above and L^2 is OH or a suitable leaving group (eg. a halogen atom such as chlorine); or

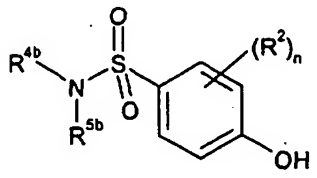
(d) preparing a compound of formula (I) wherein R^1 represents a group of formula (B) and wherein R^3 represents $-(CH_2)_q-NR^{11}R^{12}$ which comprises reacting a compound of formula (VI)



(VI)

wherein R^2, R^{4b}, R^{5b}, n and q are as defined above and L^3 represents a suitable leaving group such as a halogen atom (eg. bromine) with a compound of formula $HNR^{11}R^{12}$; wherein R^{11} and R^{12} are as defined above; or

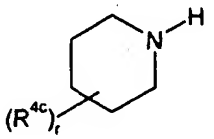
(e) preparing a compound of formula (I) wherein R^1 represents a group of formula (B) which comprises reacting a compound of formula (VII)



(VII)

wherein R^2, R^{4b}, R^{5b} and n are as defined above, with a compound of formula R^3-L^4, wherein R^3 is as defined above and L^4 represents a suitable leaving group such as a halogen atom or an OH group; or

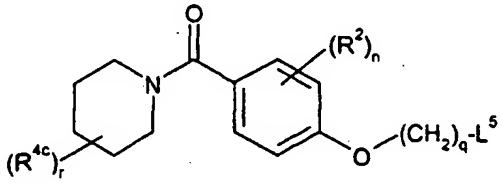
(f) preparing a compound of formula (I) wherein R^1 represents a group of formula (C) which comprises reacting a compound of formula (II) as defined above, with a compound of formula (VIII)



(VIII)

or a protected derivative thereof, wherein R^{4c} and r are as defined above; or

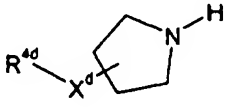
(g) preparing a compound of formula (I) wherein R^1 represents a group of formula (C) and wherein R^3 represents $-(CH_2)_q-NR^{11}R^{12}$ which comprises reacting a compound of formula (IX)



(IX)

wherein R^2, n, R^{4c}, r, and q are as defined above and L^5 represents a suitable leaving group such as a halogen atom (eg. bromine) with a compound of formula $HNR^{11}R^{12}$; wherein R^{11} and R^{12} are as defined above; or

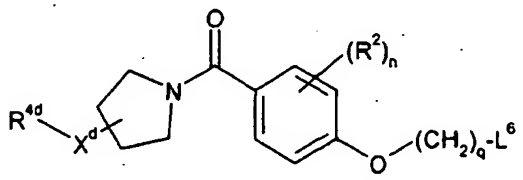
(h) preparing a compound of formula (I) wherein R^1 represents a group of formula (D) which comprises reacting a compound of formula (II) as defined above, with a compound of formula (X)



(X)

or a protected derivative thereof, wherein R^{4d} and X^d are as defined above; or

(i) preparing a compound of formula (I) wherein R^1 represents a group of formula (D) and wherein R^3 represents $-(CH_2)_q-NR^{11}R^{12}$ which comprises reacting a compound of formula (XI)

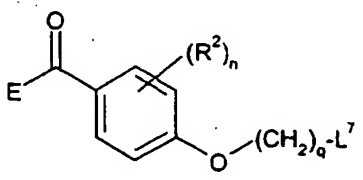


(XI)

wherein R^{4d}, X^d, R^2, n, and q are as defined above and L^6 represents a suitable leaving group such as a halogen atom (eg. bromine) with a compound of formula $HNR^{11}R^{12}$; wherein R^{11} and R^{12} are as defined above; or

(j) preparing a compound of formula (I) wherein R^1 represents a group of formula –CO-E^a, -CO-E^b or –CO-E^c which comprises reacting a compound of formula (II) as defined above, with a compound of formula H-E^a, H-E^b or H-E^c or a protected derivative thereof, wherein E^a, E^b and E^c are as defined above; or

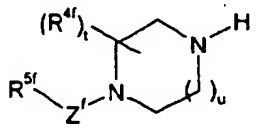
(k) preparing a compound of formula (I) wherein R^1 represents a group of formula –CO-E and wherein R^3 represents $-(CH_2)_q-NR^{11}R^{12}$ which comprises reacting a compound of formula (XII)



(XII)

wherein R^2, n, q and E are as defined above and L^7 represents a suitable leaving group such as a halogen atom (eg. bromine) with a compound of formula $HNR^{11}R^{12}$; wherein R^{11} and R^{12} are as defined above; or

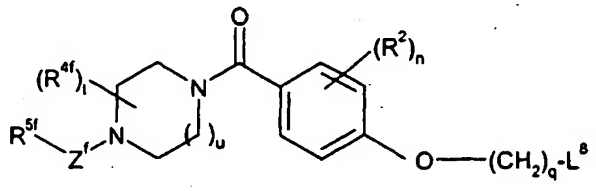
(l) preparing a compound of formula (I) wherein R^1 represents a group of formula (F) which comprises reacting a compound of formula (II) as defined above, with a compound of formula (XIII)



(XIII)

or a protected derivative thereof, wherein R^{5f}, Z^f, R^{4f}, u and t are as defined above; or

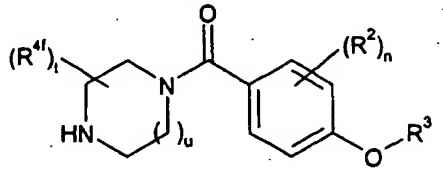
(m) preparing a compound of formula (I) wherein R^1 represents a group of formula (F) and wherein R^3 represents $-(CH_2)_q-NR^{11}R^{12}$ which comprises reacting a compound of formula (XIV)



(XIV)

wherein R^{5f}, Z^f, R^2, R^{4f}, n, t, u and q are as defined above and L^8 represents a suitable leaving group such as a halogen atom (eg. bromine) with a compound of formula $HNR^{11a}R^{12a}$; wherein R^{11a} and R^{12a} are as defined above for R^{11} and R^{12} or a group convertible thereto; or

(n) preparing a compound of formula (I) wherein R^1 represents a group of formula (F) which comprises reacting a compound of formula (XV)



(XV)

or a protected derivative thereof, wherein R^2, R^3, R^{4f}, n, t and u are as defined above, with a compound of formula R^{5fa}-Z^f-L^9, wherein R^{5fa} is as defined above for R^{5f} or a group convertible thereto, Z^f is as defined above and L^9 represents a suitable leaving group, such as a halogen atom (eg. chlorine) or a hydroxy group which may be converted into a suitable leaving group; and optionally thereafter

(o) deprotecting a compound of formula (I) which is protected; and optionally thereafter

(p) interconversion to other compounds of formula (I).

Process (a) typically comprises halogenation of the compound of formula (II) with a suitable halogenating agent (eg. thionyl chloride) followed by reaction with the compound of formula (III) in the presence of a suitable base such as triethylamine or a solid supported amine, in a suitable solvent such as dichloromethane. Process (a) may also typically comprise activation of the compound of formula (II) with a coupling reagent such as dicyclohexylcarbodiimide or solid supported carbodiimide in a suitable solvent such as N,N-dimethylformamide followed by reaction with the compound of formula (III).

Processes (b), (d), (g), (i), (k) and (m) are typically performed in the presence of a suitable solvent (such as 1-butanol) at an elevated temperature.

Process (c) typically comprises reaction with the compound of formula $R^{4b}R^{5b}NH$ optionally in the presence of a suitable base such as triethylamine or a solid supported amine, in a suitable solvent such as dichloromethane. When L^2 represents OH, process (c) typically comprises an initial halogenation reaction of the compound of formula (V) with a suitable halogenating agent (eg. thionyl chloride) prior to reaction with the compound of formula $R^{4b}R^{5b}NH$ as above.

Process (e) typically comprises an alkylation reaction under Mitsunobu conditions.

Processes (f), (h), (j) and (l) typically comprise reaction with the compound of formula (VIII), (X), H-E^a, H-E^b, H-E^c or (XIII) optionally in the presence of a suitable base such as triethylamine or a solid supported amine, in a suitable solvent such as dichloromethane. When L represents OH, processes (f), (h), (j) and (l) typically comprise an initial halogenation reaction of the compound of formula (II) with a suitable halogenating agent (eg. thionyl chloride) prior to reaction with the compound of formula (VIII), (X), H-E^a, H-E^b, H-E^c or (XIII) as above.
When L represents OH, processes (f), (h), (j) and (l) may also typically comprise activation of the compound of formula (II) with a coupling reagent such as dicyclohexylcarbodiimide or solid supported carbodiimide in a suitable solvent such as N,N-dimethylformamide followed by reaction with the compound of formula (VIII), (X), H-E^a, H-E^b, H-E^c or (XIII).

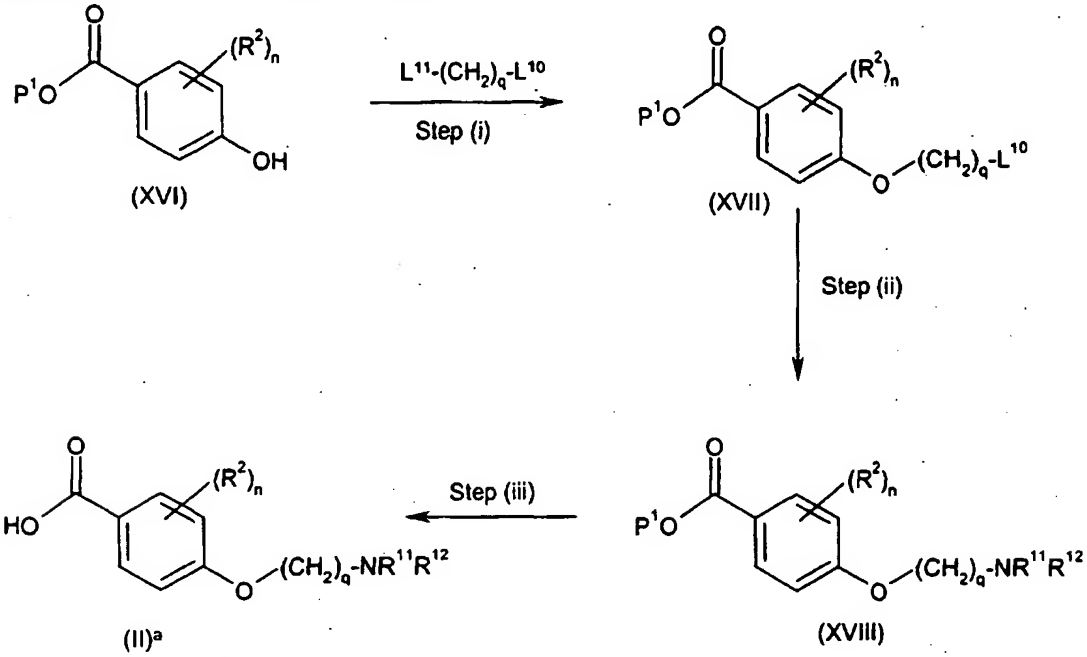
Process (n) typically comprises the use of a suitable base, such as triethylamine or a solid supported base such as diethylaminomethylpolystyrene in a suitable solvent such as dichloromethane. Process (n) may also involve activation of a carboxylic acid with a suitable coupling agent such as dicyclohexylcarbodiimide followed by reaction with the compound of formula (XV).

In process (o), examples of protecting groups and the means for their removal can be found in T. W. Greene 'Protective Groups in Organic Synthesis' (J. Wiley and Sons, 1991). Suitable amine protecting groups include sulphonyl (e.g. tosyl), acyl (e.g. acetyl, 2',2',2'-trichloroethoxycarbonyl, benzyloxycarbonyl or t-butoxycarbonyl) and arylalkyl (e.g. benzyl), which may be removed by hydrolysis (e.g. using an acid such as hydrochloric acid) or reductively (e.g. hydrogenolysis of a benzyl group or reductive removal of a 2',2',2'-trichloroethoxycarbonyl group using zinc in acetic acid) as appropriate. Other suitable amine protecting groups include trifluoroacetyl (-$COCF_3$) which may be removed by base catalysed hydrolysis or a solid phase resin bound benzyl group, such as a Merrifield resin bound 2,6-dimethoxybenzyl group (Ellman linker),

which may be removed by acid catalysed hydrolysis, for example with trifluoroacetic acid.

Process (p) may be performed using conventional interconversion procedures such as epimerisation, oxidation, reduction, alkylation, nucleophilic or electrophilic aromatic substitution, ester hydrolysis or amide bond formation.

Compounds of formula (II) wherein R^3 represents $-(CH_2)_q-NR^{11}R^{12}$ may be prepared in accordance with the following procedure:



wherein R^2, n, q, R^{11} and R^{12} are as defined above, P^1 represents a protecting group such as methyl, ethyl or t-butyl, L^{10} and L^{11} independently represent a leaving group such as halogen (eg. L^{10} represents chlorine and L^{11} represents bromine). The $-CO_2H$ group of compounds of formula $(II)^a$ may be converted to -COL wherein L represents a leaving group by, for example, halogenation using thionyl chloride.

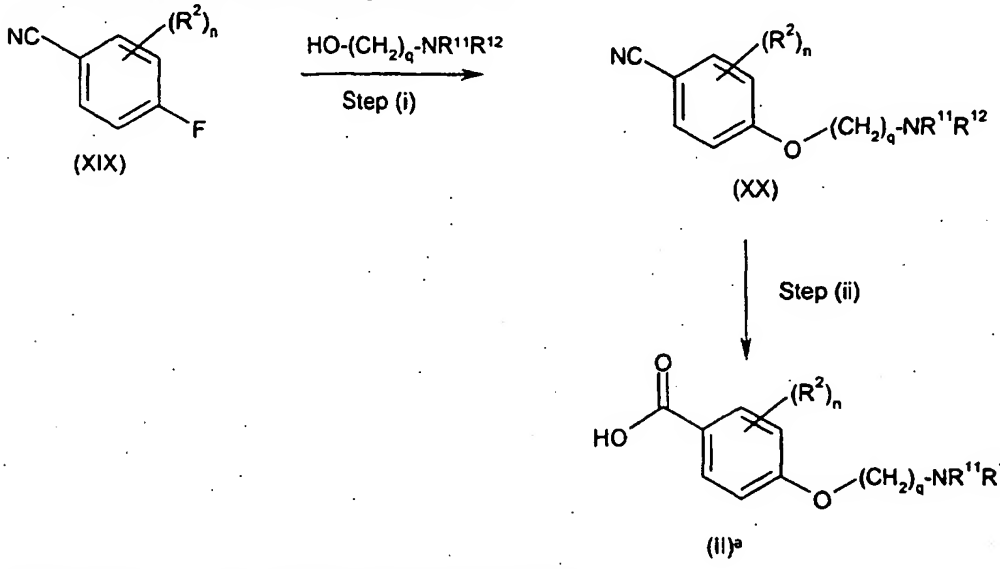
Step (i) typically comprises reaction of a compound of formula (XVI) with a suitable alkylating agent such as 1-bromo-3-chloropropane in a suitable solvent such as acetone in the presence of potassium carbonate.

Step (ii) typically comprises treatment of a compound of formula (XVII) with an amine of formula $HNR^{11}R^{12}$.

Step (iii) comprises a deprotection reaction which may be performed for example under acidic conditions with hydrochloric acid.

Compounds of formula (IV) or (XIV) may be prepared by hydrolysing a compound of formula (XVII) as defined above under suitable conditions (eg. under acidic conditions with HCl), suitably activated (eg. by conversion into the acid chloride with thionyl chloride), followed by treatment with a compound of formula (III) or (XIII), respectively as defined above.

Compounds of formula (II) wherein R^3 represents $-(CH_2)_q-NR^{11}R^{12}$ may also be prepared in accordance with the following procedure:



wherein R^2, n, q, R^{11} and R^{12} are as defined above.

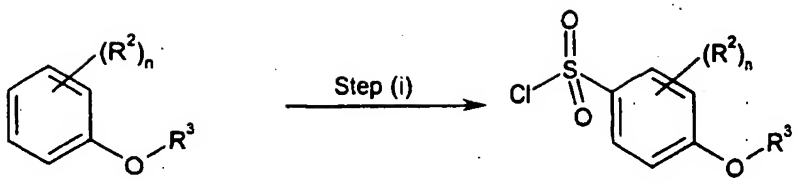
Step (i) typically comprises reaction of a compound of formula (XIX) in the presence of a suitable base such as sodium hydride in an appropriate solvent such as dimethylsulfoxide or N,N-dimethylformamide.

Step (ii) typically comprises a hydrolysis reaction for example under acidic conditions using hydrochloric acid.

Compounds of formula (IV), (IX), (XI), (XII) and (XIV) may be prepared using an analogous procedure using $HO-(CH_2)_q-L^{12}$, wherein q is as defined above and L^{12} represents an OH group or a group convertible to a leaving group.

Compounds of formula (II) wherein R^3 represents a group of formula (i) may be prepared in a similar manner to the procedure shown above.

Compounds of formula (V) wherein L^2 represents chlorine may be prepared in accordance with the following procedure:

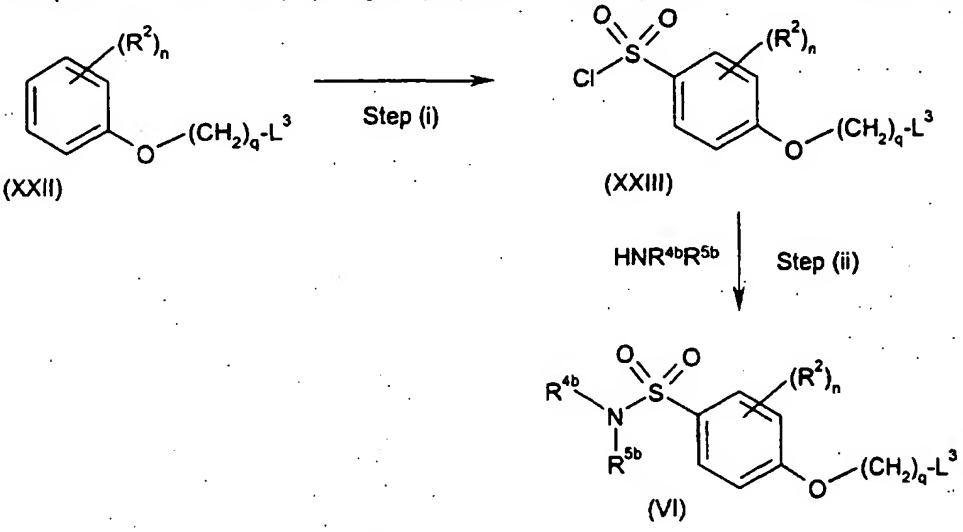


(XXI) (V)^{a}

wherein R^2, R^3 and n are as defined above.

Step (i) typically comprises reaction of a compound of formula (XXI) with a suitable reagent such as chlorosulfonic acid in a suitable solvent such as chloroform.

Compounds of formula (VI) may be prepared in accordance with the following procedure:



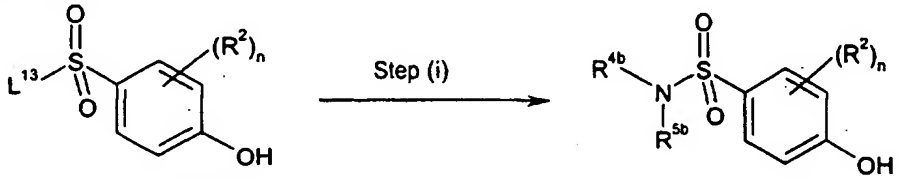
(XXII) (XXIII) (VI)

wherein R^2, n, q, L^3, R^{4b} and R^{5b} are as defined above.

Step (i) may be performed by reacting a compound of formula (XXII) with a suitable reagent such as chlorosulfonic acid in a suitable solvent such as chloroform.

Step (ii) is typically performed in the presence of a suitable solvent such as dichloromethane.

Compounds of formula (VII) may be prepared in accordance with the following procedure:



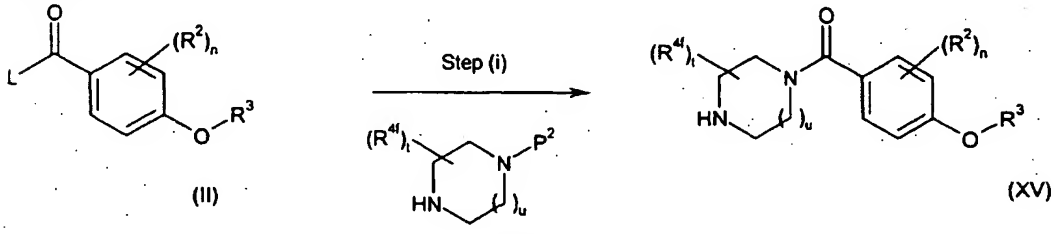
(XXIV) (VII)

wherein R^{4b}, R^{5b}, R^2 and n are as defined above and L^{13} represents a suitable leaving group such as a halogen atom (eg. chlorine).

Step (i) typically comprises reaction of a compound of formula (XXIV) with a compound of formula $R^{4b}R^{5b}NH$, wherein R^{4b} and R^{5b} are as defined above, in a suitable solvent such as dichloromethane.

Compounds of formula (VIII) are either commercially available or may be prepared via standard routes, for example, imidazolones (e.g. piperidin-4-yl-4-phenyl-1,3-dihydroimidazol-2-one) may be prepared using the procedures described by Carling *et al.*, J. Med. Chem., 1999, **42**, 2706.

Compounds of formula (XV) may be prepared in accordance with the following procedure:



(II) (XXV) (XV)

wherein L, R^2, n, R^3, R^{4f}, t and u are as defined above and P^2 represents a suitable protecting group such as t-butoxycarbonyl (t-Boc) or t-butyl.

Compounds of formula $H\text{-}E^a$, $H\text{-}E^b$ and $H\text{-}E^c$ are either commercially available or may be prepared via standard routes, for example, spiro imidazolones (e.g 3-benzyl-2-oxo-1,3,8-triazaspiro[4.5]decane) can be prepared as described by Smith *et al.*, J. Med. Chem., 1995, **38**, 3772, spiro morpholinones (e.g. 1-oxa-4,9-diazaspiro[5.5]undecan-3-one) may be prepared as described by Clark *et al.*, J. Med. Chem., 1983, **26**, 855, spiro oxazolidinones (e.g. 3-phenyl-1-oxa-3,8-diazaspiro[4.5]decan-2-one) may be prepared as described by Caroon *et al.*, J. Med. Chem., 1981, **24**, 1320.

Compounds of formula $R^{4b}R^{5b}NH$, (III), (X), (XIII), (XVI), (XIX), (XXI), (XXII), (XXIV) and (XXV) are either known in the literature or can be prepared by analogous methods.

Compounds of formula (I) and their pharmaceutically acceptable salts have affinity for and are antagonists and/or inverse agonists of the histamine H3 receptor and are believed to be of potential use in the treatment of neurological diseases including Alzheimer's disease, dementia, age-related memory dysfunction, mild cognitive impairment, cognitive deficit, epilepsy, neuropathic pain, inflammatory pain, migraine, Parkinson's disease, multiple sclerosis, stroke and sleep disorders including narcolepsy; psychiatric disorders including schizophrenia (particularly cognitive deficit of

schizophrenia), attention deficit hypereactivity disorder, depression and addiction; and other diseases including obesity, asthma, allergic rhinitis, nasal congestion, chronic obstructive pulmonary disease and gastro-intestinal disorders.

Thus the invention also provides a compound of formula (I) or a pharmaceutically acceptable salt thereof, for use as a therapeutic substance in the treatment or prophylaxis of the above disorders, in particular cognitive impairments in diseases such as Alzheimer's disease and related neurodegenerative disorders.

The invention further provides a method of treatment or prophylaxis of the above disorders, in mammals including humans, which comprises administering to the sufferer a therapeutically effective amount of a compound of formula (I) or a pharmaceutically acceptable salt thereof.

In another aspect, the invention provides the use of a compound of formula (I) or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for use in the treatment of the above disorders.

When used in therapy, the compounds of formula (I) are usually formulated in a standard pharmaceutical composition. Such compositions can be prepared using standard procedures.

Thus, the present invention further provides a pharmaceutical composition for use in the treatment of the above disorders which comprises the compound of formula (I) or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier.

The present invention further provides a pharmaceutical composition which comprises the compound of formula (I) or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier.

Compounds of formula (I) may be used in combination with other therapeutic agents, for example histamine H1 antagonists or medicaments claimed to be useful as either disease modifying or symptomatic treatments of Alzheimer's disease. Suitable examples of such other therapeutic agents may be agents known to modify cholinergic transmission such as 5-HT_6 antagonists, M1 muscarinic agonists, M2 muscarinic antagonists or acetylcholinesterase inhibitors. When the compounds are used in combination with other therapeutic agents, the compounds may be administered either sequentially or simultaneously by any convenient route.

The invention thus provides, in a further aspect, a combination comprising a compound of formula (I) or a pharmaceutically acceptable derivative thereof together with a further therapeutic agent or agents.

The combinations referred to above may conveniently be presented for use in the form of a pharmaceutical formulation and thus pharmaceutical formulations comprising a combination as defined above together with a pharmaceutically acceptable carrier or excipient comprise a further aspect of the invention. The individual components of such combinations may be administered either sequentially or simultaneously in separate or combined pharmaceutical formulations.

When a compound of formula (I) or a pharmaceutically acceptable derivative thereof is used in combination with a second therapeutic agent active against the same disease state the dose of each compound may differ from that when the compound is used alone. Appropriate doses will be readily appreciated by those skilled in the art.

A pharmaceutical composition of the invention, which may be prepared by admixture, suitably at ambient temperature and atmospheric pressure, is usually adapted for oral, parenteral or rectal administration and, as such, may be in the form of tablets, capsules, oral liquid preparations, powders, granules, lozenges, reconstitutable powders, injectable or infusible solutions or suspensions or suppositories. Orally administrable compositions are generally preferred.

Tablets and capsules for oral administration may be in unit dose form, and may contain conventional excipients, such as binding agents, fillers, tabletting lubricants, disintegrants and acceptable wetting agents. The tablets may be coated according to methods well known in normal pharmaceutical practice.

Oral liquid preparations may be in the form of, for example, aqueous or oily suspension, solutions, emulsions, syrups or elixirs, or may be in the form of a dry product for reconstitution with water or other suitable vehicle before use. Such liquid preparations may contain conventional additives such as suspending agents, emulsifying agents, non-aqueous vehicles (which may include edible oils), preservatives, and, if desired, conventional flavourings or colorants.

For parenteral administration, fluid unit dosage forms are prepared utilising a compound of the invention or pharmaceutically acceptable salt thereof and a sterile vehicle. The compound, depending on the vehicle and concentration used, can be either suspended or dissolved in the vehicle. In preparing solutions, the compound can be dissolved for injection and filter sterilised before filling into a suitable vial or ampoule and sealing. Advantageously, adjuvants such as a local anaesthetic, preservatives and buffering agents are dissolved in the vehicle. To enhance the stability, the composition can be

frozen after filling into the vial and the water removed under vacuum. Parenteral suspensions are prepared in substantially the same manner, except that the compound is suspended in the vehicle instead of being dissolved, and sterilisation cannot be accomplished by filtration. The compound can be sterilised by exposure to ethylene oxide before suspension in a sterile vehicle. Advantageously, a surfactant or wetting agent is included in the composition to facilitate uniform distribution of the compound.

The composition may contain from 0.1% to 99% by weight, preferably from 10 to 60% by weight, of the active material, depending on the method of administration. The dose of the compound used in the treatment of the aforementioned disorders will vary in the usual way with the seriousness of the disorders, the weight of the sufferer, and other similar factors. However, as a general guide suitable unit doses may be 0.05 to 1000 mg, more suitably 1.0 to 200 mg, and such unit doses may be administered more than once a day, for example two or three a day. Such therapy may extend for a number of weeks or months.

The following Descriptions and Examples illustrate the preparation of compounds of the invention.

Description 1

Ethyl 4-(3-Piperidin-1-ylpropoxy)benzoate (D1)

A stirred mixture of ethyl 4-(3-chloropropoxy)benzoate (4.73g) (D.A.Walsh *et al* J. Med. Chem. 1989, **32**(1), 105), piperidine (2.9ml), sodium carbonate (3.1g) and potassium iodide (162mg) in 1-butanol (50ml) was heated at 105° C for 16h. The reaction was cooled to rt, diluted with EtOAc (100ml), washed with water (3x50ml), saturated brine (50ml), dried ($MgSO_4$) and evaporated to give the title compound (D1) (6.88g). MS electrospray (+ion) 292 (MH^+). ^1H NMR δ ($CDCl_3$): 7.98 (2H, d, J=8.8Hz), 6.90 (2H, d, J=8.8Hz), 4.34 (2H, q ,J=7.5Hz), 4.06 (2H, t, J=6.3Hz), 2.46 (4H, m), 2.00 (2H, m), 1.50 (6H, m), 1.38 (3H, t, J=7.5Hz).

Description 2

4-(3-Piperidin-1-ylpropoxy)benzoic acid hydrochloride (D2)

A solution of ethyl 4-(3-piperidin-1-ylpropoxy)benzoate (D1) (1.4g) in concentrated hydrochloric acid (15ml) was heated under reflux for 1h, cooled and evaporated to give the title compound (D2) (1.02g). MS electrospray (+ion) 264 (MH^+). ^1H NMR δ (DMSO-d6): 10.59 (1H, s), 10.25 (1H, s), 7.90 (2H, d, J=9Hz), 7.02 (2H, d, J=9Hz), 4.14 (2H, t, J=6Hz), 3.05-3.52 (4H, m), 2.91 (2H, m), 2.20 (2H, m), 1.25-1.91 (6H, m).

Description 3

4-(3-Piperidin-1-ylpropoxy)benzoyl chloride hydrochloride (D3)

4-(3-Piperidin-1-ylpropoxy)benzoic acid hydrochloride (D2) (0.23g) in thionyl chloride (5ml) was heated under reflux for 1h. The reaction mixture was then evaporated to a

minimum and co-evaporated from DCM (3 x 10ml) to give the title compound (D3) as a white powder (0.24g).

Description 4

1-[4-(3-Piperidin-1-ylpropoxy)benzoyl]-4-t-butoxycarbonylpiperazine (D4)

To t-butoxycarbonylpiperazine (5.65g) in DCM (70ml) was added triethylamine (16.2 ml) followed by slow addition of 4-(3-piperidin-1-ylpropoxy)benzoyl chloride hydrochloride (D3) (10.60g) in DCM (100ml). The reaction was stirred at rt for 3h, then washed with saturated sodium hydrogen carbonate solution (2 x 200ml) followed by brine (100ml). The organic layer was dried ($MgSO_4$) and evaporated to a brown solid which was purified by chromatography [silica gel; 0-6% MeOH (containing 10% 0.880 ammonia solution)/DCM] to give the title compound (D4) as a pale brown solid (12.05g).

Description 5

1-[4-(3-Piperidin-1-ylpropoxy)benzoyl]piperazine dihydrochloride (D5)

To 1-[4-(3-piperidin-1-ylpropoxy)benzoyl]-4-t-butoxycarbonylpiperazine (D4) (12.05 g) in DCM (150 ml) was added 4N HCl/Dioxane (35 ml), forming a white precipitate. The reaction was stirred for 2.5 hours before evaporation. The white crude solid was triturated with DCM and dried overnight at 50°C to yield the title compound (D5) (8.26 g).

Description 6

1-[4-(3-Piperidin-1-ylpropoxy)benzoyl]-4-t-butoxycarbonylhomopiperazine (D6)

Description 6 was prepared in accordance with the procedure described for Example 172.

Description 7

1-[4-(3-Piperidin-1-ylpropoxy)benzoyl]homopiperazine dihydrochloride (D7)

To 1-[4-(3-piperidin-1-ylpropoxy)benzoyl]-4-t-butoxycarbonylhomopiperazine (D6) (1.50g) in DCM (20ml) was added 4N HCl (4ml) and the mixture was allowed to stir at rt overnight. Evaporation of solvent followed by drying under high vacuum afforded the title compound (D7) as a white solid (1.5g).

Description 8

(1S,4S)-5-[4-(3-Piperidin-1-ylpropoxy)benzoyl]-2,5-diaza-bicyclo[2.2.1] heptane-2 carboxylic acid t-butyl ester (D8)

Description 8 was prepared in accordance with the procedure described for Example 103.

Description 9

(1S,4S)-2-[4-(3-Piperidin-1-ylpropoxy)benzoyl]-2,5-diaza-bicyclo[2.2.1]heptane dihydrochloride (D9)

Description 9 was prepared in accordance with the procedure described for Example 104.

Description 10

(3R,5S)-1-[4-(3-Piperidin-1-ylpropoxy)benzoyl]-3,5-dimethylpiperazine (D10)

(2R,6S)-2,6-Dimethyl-piperazine (0.4g) was dissolved in THF (30 ml) and treated with n-butyl lithium (1.6M solution in hexanes, 4.82ml) under argon. The mixture was stirred at rt for 30min and then 4-(3-piperidin-1-ylpropoxy)benzoyl chloride hydrochloride (D3) (1.0g), dissolved in DCM (10ml), was added dropwise. The reaction was stirred for 1h and then evaporated to a minimum and the crude residue purified by column chromatography [silica gel, eluted with 0-10% MeOH (containing 10% 0.880 ammonia solution) in DCM] to afford the title compound (D10) as a yellow oil (0.65 g).

Description 11

(S)-N-[4-(3-Piperidin-1-ylpropoxy)benzoyl]-3-aminopyrrolidine dihydrochloride (D11)

A solution of 4-(3-piperidin-1-ylpropoxy)benzoic acid hydrochloride (D2) (515mg) in thionyl chloride (10ml) was refluxed for 1h, cooled to rt and evaporated. The acid chloride was re-evaporated from DCM (2x10ml). The residue was redissolved in DCM (5ml) and triethylamine (0.67ml) and added to an ice cold stirred solution of (S)-3-t-butoxycarbonylaminopyrrolidine (304mg) The solution was allowed to gain rt, stirred for 1h. and then chromatographed (silica gel, step gradient 2-6% MeOH in DCM). Fractions containing the required product were treated with excess hydrogen chloride (4M solution in dioxan) for 2h and then concentrated to yield the title compound (D11) (650mg). MS electrospray (+ion) 332 (MH^+). ^1H NMR δ (DMSO-d6), 10.38 (1H, s), 8.40 (3H, s), 7.52 (2H, d, J=9Hz), 6.99 (2H, d, J=9Hz), 4.11 (2H, t, 6Hz), 2.75-3.92 (11H, m), 2.85 (2H, m), 1.90-2.30 (4H, m), 1.38-1.88 (6H, m).

Description 12

1-Bromo-3-(4-chlorosulfonylphenoxy)propane (D12)

A stirred solution of 3-bromo-1-phenoxypropane (4.3g) in chloroform (20ml) at –5°C was treated dropwise with a solution of chlorosulfonic acid (2.66ml) in chloroform keeping the temperature below 0°C. The reaction was stirred for 5 min then allowed to gain rt and stirred for 4 days. The mixture was poured onto ice and allowed to gain rt. The organic layer was collected, washed with water (3x20ml), saturated brine (20ml), dried ($MgSO_4$) and evaporated to give the title compound (D12) (1.9g). ^1H NMR δ ($CDCl_3$): 7.98 (2H, d, J=8.8Hz), 7.05 (2H, d, J=8.8Hz), 4.24 (2H, t, J=5.8Hz), 3.61 (2H, t, J=5.8Hz), 2.37 (2H, m).

Description 13

4-[4-(3-Bromopropoxy)benzenesulfonyl]morpholine (D13)

A solution of 1-bromo-3-(4-chlorosulfonylphenoxy)propane (D12) (200mg) in DCM (5ml) was treated with morpholine (0.14ml) and stirred for 1h. The solution was chromatographed (silica, step gradient 15 to 30% EtOAc in light petroleum 40°-60°) to give the title compound (D13) (99mg). MS electrospray (+ion) 365 (MH^+). ^1H NMR δ ($CDCl_3$): 7.69 (2H, d, J=9Hz), 7.02 (2H, d, J=9Hz), 4.19 (2H, t, J=5.8Hz), 3.74 (4H, m), 3.61 (2H, t, J=5.8Hz), 2.99 (4H, m), 2.36 (2H, m).

Description 14

4-(3-Piperidin-1-yl-propoxy)-2-trifluoromethyl-benzonitrile (D14)

4-Fluoro-2-trifluoromethyl-benzonitrile (1.20g) was dissolved in THF (20ml) and 3-piperidin-1-yl-propan-1-ol (0.91ml) was added. The reaction was cooled to 0°C and potassium hexamethyldisilazide (0.5M solution in toluene; 12.72ml) was added dropwise. The reaction was stirred at rt overnight, then diluted with ethyl acetate (50ml) and partitioned with aqueous 1N HCl (50ml). The aqueous layer was washed with ethyl acetate (50ml), then basified to pH 8.0 with sodium hydrogen carbonate and extracted with ethyl acetate (3x75ml). The combined organic extracts were dried ($MgSO_4$) and evaporated to give the title compound (D14) as a clear oil which crystallised on standing (0.80g).

Description 15

4-(3-Piperidin-1-yl-propoxy)-2-trifluoromethyl-benzoic acid hydrochloride (D15)

4-(3-Piperidin-1-yl-propoxy)-2-trifluoromethyl-benzonitrile (D14) (0.80 g) was dissolved in conc. HCl (20ml) and heated at 135°C for 24h. Concentrated sulfuric acid (10ml) was added and the reaction heated at 135°C for 36h. The reaction mixture was then evaporated to a minimum and treated with 12.5 N sodium hydroxide solution until pH 12 was obtained. The mixture was filtered and the filtrate evaporated to a minimum. Conc. HCl was then added until pH 1. The mixture was evaporated and the solid residue was extracted several times with methanol. The combined extracts were evaporated to give the title compound (D15) as a white solid (0.90g).

Description 16

4-(3-Piperidin-1-yl-propoxy)-2-trifluoromethyl-benzoyl chloride hydrochloride (D16)

4-(3-Piperidin-1-yl-propoxy)-2-trifluoromethyl-benzoic acid hydrochloride (D15) (0.9g) was heated at reflux in thionyl chloride (20ml) for 2h. The reaction mixture was evaporated to a minimum then co-evaporated with DCM (3x) to give the title compound (D16) as a white solid (1.0g)

Description 17

2,5-Difluoro-4-(3-piperidin-1-yl)propoxy)benzonitrile (D17)

The title compound was prepared using the method of Description 14 from 2,4,5-trifluorobenzonitrile.

Description 18

2,5-Difluoro-4-(3-piperidin-1-ylpropoxy)benzoic acid hydrochloride (D18)

2,5-Difluoro-4-(3-piperidin-1-ylpropoxy)benzonitrile (D17) (1.1g) was dissolved in conc. HCl and heated under reflux for 24h. The reaction mixture was then cooled to 5°C and the resultant precipitate filtered and dried at 50°C under high vacuum to give the title compound (D18) (0.56g).

Description 19

2,5-Difluoro-4-(3-piperidin-1-ylpropoxy)benzoyl chloride hydrochloride (D19)

The title compound was prepared from 2,5-difluoro-4-(3-piperidin-1-yl)propoxy)benzoic acid hydrochloride (D18) using the method of Description 16.

Description 20

2-Fluoro-4-(3-piperidin-1-ylpropoxy)benzonitrile (D20)

The title compound was prepared using the method of Description 14 from 2,4-difluorobenzonitrile.

Description 21

2-Fluoro-4-(3-piperidin-1-ylpropoxy)benzoic acid hydrochloride (D21)

2-Fluoro-4-(3-piperidin-1-ylpropoxy)benzonitrile (D20) (1.4g) was dissolved conc. HCl and heated under reflux for 24h. The reaction mixture was then cooled to 5°C and the resultant precipitate filtered and dried at 50°C under high vacuum to give the title compound (D21) (1.5g).

Description 22

2-Fluoro-4-(3-piperidin-1-ylpropoxy)benzoyl chloride hydrochloride (D22)

The title compound was prepared from 2-fluoro-4-(3-piperidin-1-ylpropoxy) benzoic acid hydrochloride (D21) using the method of Description 16.

Description 23

1-tert-Butoxycarbonyl-4-[4-fluoro-2-trifluoromethyl-benzoyl]piperazine (D23)

4-Fluoro-2-(trifluoromethyl)benzoic acid (2.0g) was dissolved in thionyl chloride (20ml) and heated at reflux for 2h. The reaction was then cooled and evaporated (co-evaporated with DCM x 3) and then dissolved in DCM (50ml). This solution was added slowly to 1-tert-butoxy-carbonylpiperazine (1.62g), and TEA (2.54ml), dissolved in DCM (50ml). The reaction was then stirred at rt for 2h before being washed with 1N HCl (2x100ml), saturated sodium hydrogen carbonate (2x100ml) and brine (50ml). The organic layer was dried ($MgSO_4$) and evaporated to give the title compound (D23) (3.09g).

Description 24

1-tert-Butoxycarbonyl-4-[4-(3-piperidin-1-ylpropoxy)-2-trifluoromethyl-benzoyl]piperazine (D24)

1-tert-Butoxycarbonyl-4-[4-fluoro-2-trifluoromethyl-benzoyl]piperazine (D23) (2.05g) and 3-(1-piperidinyl)-1-propanol (1.17g) were dissolved in DMSO (30ml) and KHMDS (12.2ml, 20% in THF) was added slowly and the reaction was stirred for 30min. The reaction mixture was then evaporated and re-dissolved in ethyl acetate and washed with saturated sodium hydrogen carbonate (2x80ml) and brine (80ml). The organic layer was dried ($MgSO_4$) and evaporated, and the residue purified by chromatography [silica gel;gradient elution with 0-10% MeOH (containing 10% 0.880 ammonia solution)/DCM]. Pure product fractions were evaporated and dried under high vacuum to give the title compound (D24) as a white solid (2.15g).

Description 25

1-[4-(3-piperidin-1-ylpropoxy)-2-trifluoromethyl-benzoyl]piperazine dihydrochloride (D25)

1-tert-Butoxycarbonyl-4-[4-(3-piperidin-1-ylpropoxy)-2-trifluoromethyl-benzoyl]piperazine (D24) (2.15g) was dissolved in DCM (50ml) and 4N HCl in dioxane (25 ml) was added and the reaction stirred at rt overnight. The reaction mixture was then evaporated [co-evaporated with toluene (3x) , then acetone (3x)] to give the title compound (D25) as a white foam (1.82g).

Description 26

(3*R*,5*S*)-1-tert-Butoxycarbonyl-3,5-dimethyl-4-(4-fluorobenzoyl)piperazine dihydrochloride (D26)

(2*R*,6*S*)-2,6-Dimethylpiperazine (0.9g) was stirred in THF (50ml) and n-butyl lithium (2.5M in hexanes) (6.9ml) was added. The mixture was stirred for 30min and then TMSCl (1.1ml) was added. The reaction was stirred for a further 30min and then 4-fluorobenzoyl chloride (1.0g) in THF (5 ml) was added dropwise and the reaction stirred for a further 30min. Methanol (10ml) was then added and the reaction evaporated to dryness. The crude amine intermediate was dissolved in DCM (30ml) and TEA (1.23ml) was added followed by di-*tert*-butyl dicarbonate (1.7g) and the reaction stirred at rt under argon overnight. The mixture was then washed with saturated sodium hydrogen carbonate (3x50ml) and brine (50ml), dried ($MgSO_4$) and evaporated to yield the crude product which was purified by column chromatography [silica gel; gradient elution;0-100% EtOAc:Hexane]. Fractions containing pure product were evaporated to give the title compound (D26) (0.67g).

Description 27

(3*R*,5*S*)-1-tert-Butoxycarbonyl-3,5-dimethyl-4-[4-(3-piperidin-1-yl)propoxybenzoyl]piperazine dihydrochloride (D27)

(3*R*,5*S*)-1-tert-Butoxycarbonyl-3,5-dimethyl-4-(4-fluorobenzoyl)piperazine dihydrochloride (D26) (0.56g) was dissolved in DMSO (5ml) and 3-(1-piperidinyl)-1-

propanol (0.24g) was added followed by dropwise addition of KHMDS (0.5 M in toluene) (3.3ml), and the reaction was stirred at rt under argon for 2h. The reaction mixture was then evaporated and redissolved in ethyl acetate (100ml), washed with saturated sodium hydrogen carbonate (3x 50ml), brine (50ml) and dried ($MgSO_4$) before being evaporated. The crude product was chromatographed [silica gel, gradient elution, 0-10% MeOH (containing 10% 0.880 ammonia solution)/DCM]. Pure product fractions were evaporated to give the title compound (D27) as a clear oil (0.2g).

Description 28

(2*R*,6*S*)-2,6-Dimethyl-1-[4-(3-piperidin-1-yl)propoxybenzoyl]piperazine dihydrochloride (D28)

(3*R*,5*S*)-1-tert-Butoxycarbonyl-3,5-dimethyl-4-[4-(3-piperidin-1-yl)propoxybenzoyl]piperazine dihydrochloride (D27) (0.2g) was dissolved in DCM (5ml) and 4N HCl/dioxane (5ml) was added and the reaction stirred for 16h. The reaction mixture was then evaporated (co-evaporated with toluene 3x) to give the title compound (D28) as a white powder (0.18g).

Description 29

4-[(1-tert-Butoxycarbonyl-4-piperidinyl)oxy]benzonitrile (D29)

4-Fluorobenzonitrile (3.0g) was dissolved in THF (50ml) and then N-tert-butoxy-carbonyl-4-piperidinol (4.98g) was added. Potassium hexamethyldisilazide (20% wt solution in THF, 24.62g) was then added dropwise and the reaction stirred at rt for 2h. The reaction mixture was then evaporated to a minimum, redissolved in EtOAc (100 ml) and washed with aqueous 1N HCl (2x100 ml), saturated sodium bicarbonate solution (2x100ml) and brine (100 ml). The organic layer was dried ($MgSO_4$) and then purified by chromatography [silica gel, step gradient 0-60% EtOAc/Hexane]. Fractions containing the required product were evaporated to give the title compound (D29) as a clear oil which crystallised on standing (6.83g). ^{1}H NMR δ ($CDCl_3$): 7.59 (2H, d, J=7.50Hz), 6.95 (2H, d, J=7.50Hz), 4.44 (1H, m), 3.70 (2H, m), 3.38 (2H, m), 1.91 (2H, m), 1.77 (2H, m), 1.47 (9H, s).

Description 30

4-(4-Piperidinyloxy)benzonitrile trifluoroacetate (D30)

4-[(1-tert-Butoxycarbonyl-4-piperidinyl)oxy]benzonitrile (D29) (6.83g) was dissolved in DCM (30ml) and TFA (30 ml) was added. The reaction was stirred at rt for 1h and then evaporated to give the title compound (D30) as a yellow oil (7.15g – TFA salt plus 1.3 equivalents of TFA).

Description 31

4-[(1-Cyclobutyl-4-piperidinyl)oxy]benzonitrile (D31)

4-(4-Piperidinyloxy)benzonitrile trifluoroacetate (D30) (2.2g) was dissolved in DCM (50ml) and triethylamine (1.92ml) was added followed by cyclobutanone (0.64g). The

mixture was stirred for 5min, then sodium triacetoxyborohydride (1.94g) was added and the reaction was stirred at rt under argon overnight. The reaction mixture was then washed with saturated potassium carbonate solution (3x30ml) and brine (30ml). The organic layer was dried ($MgSO_4$) and evaporated to give the title compound (D31) as a white solid (1.91g). ^1H NMR δ ($CDCl_3$): 7.56 (2H, d, J=6.84Hz), 6.93 (2H, d, J=6.80Hz), 4.41 (1H, m), 2.77 (1H, m), 2.75 (2H, m), 2.30 (2H, m), 2.06 (4H, m), 1.87 (4H, m), 1.66 (2H, m).

Description 32

4-[(1-Isopropyl-4-piperidinyl)oxy]benzonitrile (D32)

The title compound was prepared in a similar manner to Description 31 using acetone in place of cyclobutanone.

Description 33

4-[(1-Cyclopentyl-4-piperidinyl)oxy]benzonitrile (D33)

The title compound was prepared in a similar manner to Description 31 using cyclopentanone in place of cyclobutanone.

Description 34

4-[(1-Cyclobutyl-4-piperidinyl)oxy]benzoic acid hydrochloride (D34)

4-[(1-Cyclobutyl-4-piperidinyl)oxy]benzonitrile (D31) (1.91g) was dissolved in conc. HCl (30ml) and heated to 120°C for 2h. The reaction mixture was then allowed to cool to rt and then further cooled to 5°C. The resultant white precipitate was filtered off and washed with a small quantity of water. The solid was then dried at 50°C under vacuum overnight to yield the title compound (D34) as a white powder (0.95g). ^1H NMR δ (DMSO-d6): 12.60 (1H, s), 10.96 (1H, s), 7.90 (2H, d, J=8.70Hz), 7.09 (2H, d, J=8.60Hz), 4.09-4.64 (1H, m), 3.66-3.15 (3H, m), 2.99-2.77 (2H, m), 2.48-1.60 (10H, m).

Description 35

4-[(1-Cyclobutyl-4-piperidinyl)oxy]benzoyl chloride hydrochloride (D35)

4-[(1-Cyclobutyl-4-piperidinyl)oxy]benzoic acid hydrochloride (D34) (0.20g) was dissolved in thionyl chloride (10 ml) and heated under reflux for 1.5h. The thionyl chloride was removed by evaporation and the residue evaporated from DCM (3x10ml) to give the title compound (D35) (0.21g).

Description 36

4-[(1-Cyclobutyl-4-piperidinyl)oxy]benzoyl]-4-t-butoxycarbonylpiperazine (D36)

To t-butoxycarbonylpiperazine (0.62g) in DCM (50ml) was added triethylamine (1.3ml) followed by slow addition of 4-[(1-cyclobutyl-4-piperidinyl)oxy]benzoyl chloride hydrochloride (D35) (1.16g) in DCM (50ml). The reaction was stirred at rt for 16h, then washed with saturated sodium hydrogen carbonate solution (3x50ml) followed by brine (50ml). The organic layer was dried ($MgSO_4$) and evaporated to a brown solid which was

purified by chromatography [silica gel; step gradient 0-10% MeOH (containing 10% 0.880 ammonia solution)/DCM] to give the title compound (D36) as a pale brown solid (1.0g).

Description 37

4-[(1-Cyclobutyl-4-piperidinyl)oxy]benzoyl]piperazine dihydrochloride (D37)

To 4-[(1-cyclobutyl-4-piperidinyl)oxy]benzoyl]-4-t-butoxycarbonylpiperazine (D36) (1.0g) in DCM (30ml) was added 1N HCl in diethyl ether (30ml), forming a white precipitate. The reaction was stirred for 16h before evaporation. The white crude solid was dried overnight at 50°C to yield the title compound (D37) (0.87g).

Description 38

4-[(1-Isopropyl-4-piperidinyl)oxy]benzoyl]piperazine dihydrochloride (D38)

The title compound was prepared from 4-[(1-isopropyl-4-piperidinyl)oxy] benzonitrile (D32) following the procedures in Descriptions 34-37.

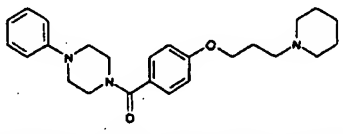
Description 39

4-[(1-Cyclopentyl-4-piperidinyl)oxy]benzoyl]piperazine dihydrochloride (D39)

The title compound was prepared from 4-[(1-cyclopentyl-4-piperidinyl)oxy] benzonitrile (D33) following the procedures in Descriptions 34-37.

Example 1

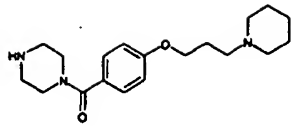
N-[4-(3-Piperidin-1-ylpropoxy)benzoyl]-4-phenylpiperazine dihydrochloride (E1)



A solution of 4-(3-piperidin-1-ylpropoxy)benzoic acid hydrochloride (D2) (500mg) in thionyl chloride (5ml) was refluxed for 1h, cooled to rt and evaporated. The acid chloride was re-evaporated from DCM (2x10ml). The residue was redissolved in DCM (5ml) and triethylamine (0.7ml) and added to a stirred solution of 4-phenylpiperazine (270mg) in DCM (20ml) at rt. The mixture was stirred for 1h, washed with saturated sodium hydrogen carbonate solution (10ml), water (3x10ml), dried ($MgSO_4$) and evaporated. The residue was chromatographed (silica gel, step gradient 2-6% MeOH in DCM). Fractions containing the required product were treated with excess hydrogen chloride (4M solution in dioxan) and then concentrated to yield the title compound (E1) (630mg). MS electrospray (+ion) 408 (MH^+). ^1H NMR δ (DMSO-d6): 10.39 (1H,s), 6.90-7.47 (9H, m), 4.11 (2H, t, J=6Hz), 2.66-3.89 (12H, m), 2.24 (2H, m), 1.22-1.83 (6H, m).

Example 2

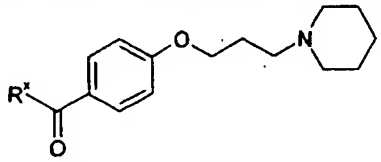
N-[4-(3-Piperidin-1-ylpropoxy)benzoyl]piperazine dihydrochloride (E2)

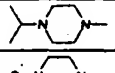
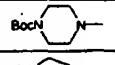
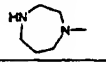


4-(3-Piperidin-1-ylpropoxy)benzoic acid hydrochloride (D2) (150mg) was converted to the title compound (E2) by reaction with 4-t-butoxycarbonylpiperazine (93mg) using the method described in Example 1 (E1) except that the treatment with excess hydrogen chloride (4M solution in dioxan) was continued for 2h before evaporation (yield = 125mg). MS electrospray (+ion) 332 (MH^+). ^1H NMR δ (DMSO-d6), 10.51 (1H, s), 9.50 (1H, s), 7.44 (2H, d, J=8.8Hz), 7.00 (2H, d, J=8.8Hz), 4.11 (2H, t, J=6Hz), 3.71 (4H, m), 3.35 (8H, m), 2.87 (2H, m), 2.22 (2H, m), 1.30-1.90 (6H, m).

Examples 3-5 (E3-5)

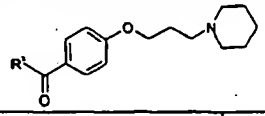
Examples 3 – 5 were prepared from 4-(3-piperidin-1-ylpropoxy)benzoic acid hydrochloride (D2) and the appropriate amine using the method outlined in Example 1 (E1) and displayed ^1H NMR and mass spectral data that were consistent with structure.

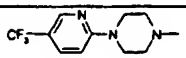
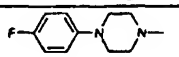
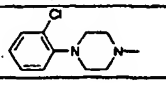


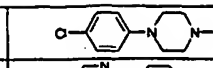
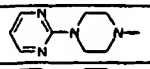
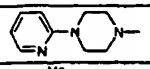
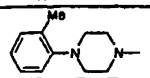
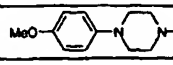
Example No	R^x	Mass Spectrum (ES^+)
E3		374 $[M+H]^+$
E4		432 $[M+H]^+$
E5		346 $[M+H]^+$

Examples 6-13 (E6-13)

Examples 6–13 were prepared from 4-(3-piperidin-1-ylpropoxy)benzoic acid hydrochloride (D2) and the appropriate amine using the method outlined in Example 1 (E1) with the exception that polymer supported base was employed. All compounds displayed ^1H NMR and mass spectral data that were consistent with structure.

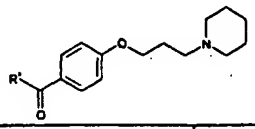


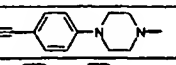
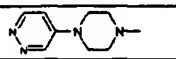
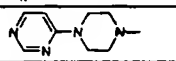
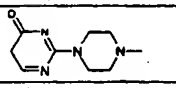
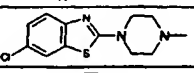
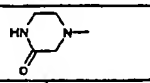
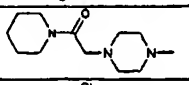
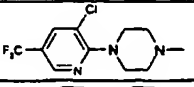
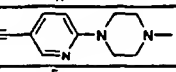
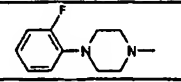
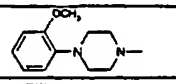
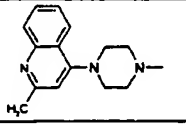
Example No	R^x	Mass Spectrum
E6		477 $[M+H]^+$
E7		426 $[M+H]^+$
E8		442, 444 $[M+H]^+$

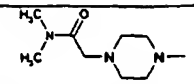
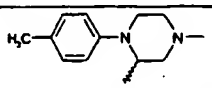
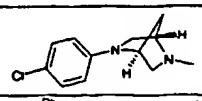
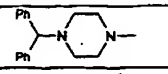
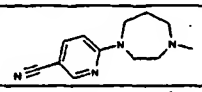
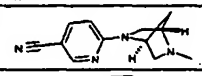
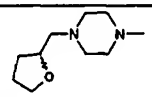
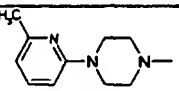
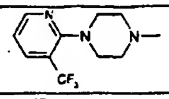
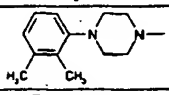
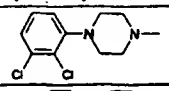
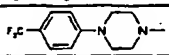
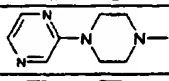
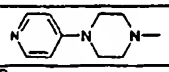
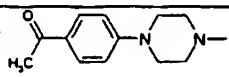
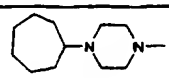
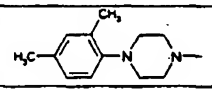
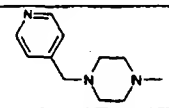
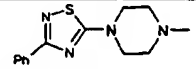
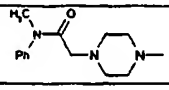
E9		442, 444 $[M+H]^+$
E10		410 $[M+H]^+$
E11		409 $[M+H]^+$
E12		422 $[M+H]^+$
E13		438 $[M+H]^+$

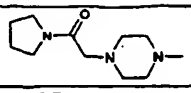
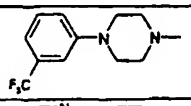
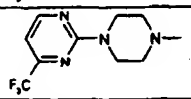
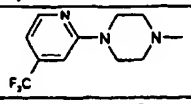
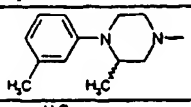
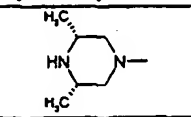
Examples 14-51 (E14-51)

Examples 14-51 were prepared from 4-(3-piperidin-1-ylpropoxy)benzoic acid hydrochloride (D2) and the appropriate amine using the method outlined in Example 1 (E1) with the exception that diethylaminomethylpolystyrene was employed as the base. All compounds displayed ^1H NMR and mass spectral data that were consistent with structure.



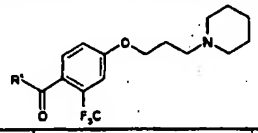
Example No	R^x	Mass Spectrum	
E14		433 $[M+H]^+$	
E15		410 $[M+H]^+$	
E16		410 $[M+H]^+$	
E17		426 $[M+H]^+$	
E18		500/502 $[M+H]^+$	
E19		346 $[M+H]^+$	
E20		457 $[M+H]^+$	
E21		511/513 $[M+H]^+$	
E22		434 $[M+H]^+$	
E23		425 $[M+H]^+$	
E24		438 $[M+H]^+$	
E25		473 $[M+H]^+$	

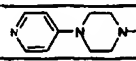
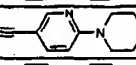
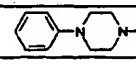
E26		417 [M+H]$^+$	
E27		436 [M+H]$^+$	
E28		455/457 [M+H]$^+$	
E29		498 [M+H]$^+$	
E30		448 [M+H]$^+$	
E31		446 [M+H]$^+$	
E32		416 [M+H]$^+$	
E33		422 [M+H]$^+$	
E34		477 [M+H]$^+$	
E35		436 [M+H]$^+$	
E36		477/479/481 [M+H]$^+$	
E37		476 [M+H]$^+$	
E38		410 [M+H]$^+$	
E39		409 [M+H]$^+$	
E40		450 [M+H]$^+$	
E41		428 [M+H]$^+$	
E42		436 [M+H]$^+$	
E43		423 [M+H]$^+$	
E44		492 [M+H]$^+$	
E45		479 [M+H]$^+$	

E46		443	$[M+H]^+$
E47		476	$[M+H]^+$
E48		478	$[M+H]^+$
E49		477	$[M+H]^+$
E50		436	$[M+H]^+$
E51		360	$[M+H]^+$

Examples 52-54 (E52-E54)

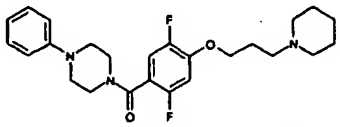
Examples 52-54 (E52-E54) were prepared from 4-(3-piperidin-1-yl-propoxy)-2-trifluoromethyl-benzoyl chloride (D16) and the appropriate aryl piperazine according to the method described in Example 1 except that diethylaminomethyl polystyrene was employed as the base. The final products were purified by chromatography, and converted to the corresponding HCl salts with 1M HCl in diethyl ether. All compounds displayed ^1H NMR and mass spectral data that were consistent with structure.



Example No	R^x	Mass Spectrum
E52		477 $[M+H]^+$
E53		502 $[M+H]^+$
E54		476 $[M+H]^+$

Example 55

N-[2,5-Difluoro-4-(3-piperidin-1-ylpropoxy)benzoyl]-4-phenylpiperazine dihydrochloride (E55)

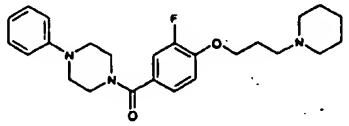


The title compound was prepared from 2,5-difluoro-4-(3-piperidin-1-ylpropoxy)benzoyl chloride hydrochloride (D19) and 4-phenylpiperazine according to the method described in Example 1 except that diethylaminomethyl polystyrene was employed as the base.

MS electrospray (+ion) 444 (MH^+).

Example 56

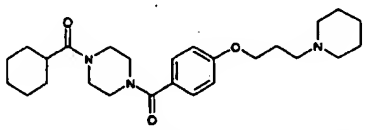
N-[2-Fluoro-4-(3-Piperidin-1-ylpropoxy)benzoyl]-4-phenylpiperazine dihydrochloride (E56)



The title compound was prepared from 2-fluoro-4-(3-piperidin-1-ylpropoxy)benzoyl chloride hydrochloride (D22) and 4-phenylpiperazine according to the method described in Example 1 except that diethylaminomethyl polystyrene was employed as the base. MS electrospray (+ion) 426 (MH^+).

Example 57

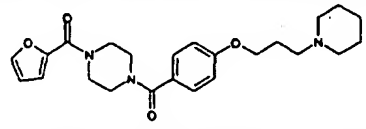
1-[4-(3-Piperidin-1-ylpropoxy)benzoyl]-4-(1-cyclohexanecarbonyl)-piperazine hydrochloride (E57)



To 4-(3-piperidin-1-ylpropoxy)benzoyl chloride hydrochloride (D3) (0.24g) in DCM (10 ml) was added 1-(cyclohexanecarbonyl)-piperazine (0.155 g) and diethylaminomethyl polystyrene (3.2mmol/g, 0.69g). The mixture was stirred for 16h. The reaction mixture was then loaded directly onto a silica column and eluted with 0-10% MeOH (containing 10% 0.880 ammonia solution) in DCM. The isolated free base was dissolved in DCM (5ml) and treated with 4N HCl/Dioxane solution (1ml) with stirring for 10min. The reaction was concentrated, and the residue co-evaporated with toluene (3x10ml) and then dried at 50°C under high vacuum for 16h to yield the title compound (E57) as a pale solid (0.165g). MS electrospray (+ion)-442 (MH^+). ^1H NMR δ (DMSO-d6): 9.71 (s, 1H), 7.39 (d, 2H, J=6.84Hz), 7.00 (d, 2H, J=6.84Hz), 4.10 (m, 2H), 3.47-3.25 (m, 10H), 3.16 (m, 2H), 2.90 (m, 2H), 2.55 (m, 1H), 2.19 (m, 2H), 1.82-1.62 (m, 10H), 1.40-1.16 (m, 6H).

Example 58

1-[4-(3-Piperidin-1-ylpropoxy)benzoyl]-4-(2-furoyl)-piperazine hydrochloride (E58)

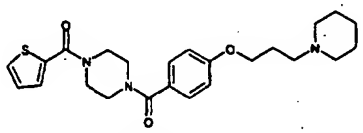


The title compound was prepared from 4-(3-piperidin-1-ylpropoxy)benzoyl chloride hydrochloride (D3) (0.24g) and 1-(2-furoyl)piperazine (0.12g) using the procedure described for Example 1 and isolated as a pale yellow solid (0.16g). MS electrospray (+ion) 426 (MH^+). ^1H NMR δ (DMSO-d6): 9.80 (s, 1H), 7.84 (s, 1H), 7.43 (d, 2H,

J=6.80Hz), 7.03 (m, 1H), 7.02 (d, 2H, J=6.80Hz), 6.63 (m, 1H), 4.11 (m, 1H), 3.72-3.45 (m, 10H), 3.16 (m, 2H), 2.90 (m, 2H), 2.18 (m, 2H), 1.82-1.40 (m, 6H).

Example 59

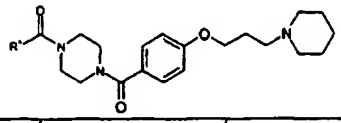
1-[4-(3-Piperidin-1-ylpropoxy)benzoyl]-4-(thiophen-2-carbonyl)-piperazine hydrochloride (E59)

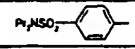
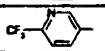
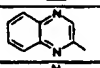
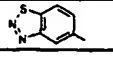


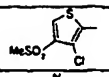
1-[4-(3-Piperidin-1-ylpropoxy)benzoyl]piperazine dihydrochloride (D5) (0.15g) was stirred with diethylaminomethyl polystyrene (3.2mmol/g, 0.35g) in DCM (10 ml) and thiophen-2-carbonyl chloride (0.057g) was added. The reaction was stirred for 16h and then loaded directly onto a silica column, eluting with 0-10% MeOH (containing 10% 0.880 ammonia solution)/DCM. The isolated free base product was then dissolved in DCM (5ml) and treated with 4N HCl/Dioxane solution (1 ml) and stirred for 10 min. The reaction was concentrated, and the residue co-evaporated with toluene (3 x 10ml) then dried at 50°C under high vacuum for 16h to yield the title compound (E59) as a pale yellow solid (0.14g). MS electrospray (+ion) 442 (MH^+). ^1H NMR δ (DMSO-d6): 9.85 (s, 1H), 7.77 (m, 1H), 7.44 (m, 3H), 7.13 (m, 1H), 7.01 (d, 2H, 8.72Hz), 4.10 (m, 2H), 3.70-3.34 (m, 10H), 3.17 (m, 1H), 2.89 (m, 2H), 2.17 (m, 2H), 1.79-1.37 (m, 6H).

Examples 60-74 (E60-E74)

Examples 60-74 were prepared from 1-[4-(3-piperidin-1-ylpropoxy)benzoyl]piperazine dihydrochloride (D5) and the appropriate acid chloride using the procedure described in Example 59 and displayed ^1H NMR and mass spectral data that were consistent with structure.

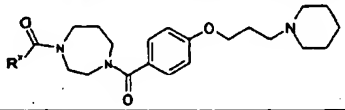


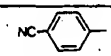
Example No	R^x	Mass Spectrum (ES^+)
E60		$[M+H]^+$ 461
E61		$[M+H]^+$ 461
E62		$[M+H]^+$ 600
E63		$[M+H]^+$ 437
E64		$[M+H]^+$ 505
E65		$[M+H]^+$ 488
E66		$[M+H]^+$ 452
E67		$[M+H]^+$ 494

E68		$[M+H]^+$ 555
E69		$[M+H]^+$ 455
E70		$[M+H]^+$ 427
E71		$[M+H]^+$ 496
E72		$[M+H]^+$ 454
E73		$[M+H]^+$ 496
E74		$[M+H]^+$ 496

Examples 75-77 (E75-E77)

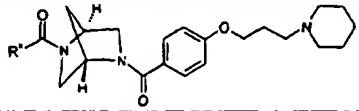
Examples 75-77 were prepared from 1-[4-(3-piperidin-1-ylpropoxy)benzoyl]homopiperazine dihydrochloride (D7) and the appropriate carboxylic acid chloride or carbamoyl chloride following the procedure described for Example 59 and displayed ^{1}H NMR and mass spectral data that were consistent with structure.

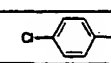
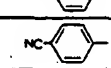


Example No	R^x	Mass Spectrum (ES^+)
E75		$[M+H]^+$ 475
E76		$[M+H]^+$ 475
E77		$[M+H]^+$ 459

Examples 78 and 79 (E78-E79)

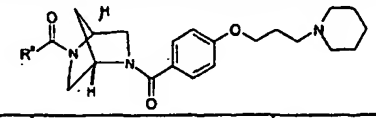
Examples 78 and 79 were prepared from (1S,4S)-2-[4-(3-piperidin-1-ylpropoxy)benzoyl]-2,5-diaza-bicyclo[2.2.1] heptane dihydrochloride (D9) and the appropriate acid chloride following the procedure described for Example 59 and displayed ^{1}H NMR and mass spectral data that were consistent with structure.



Example No	R^x	Mass Spectrum (ES^+)
E78		$[M+H]^+$ 483
E79		$[M+H]^+$ 473

Examples 80 and 81 (E80-E81)

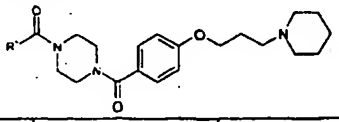
Examples 80 and 81 were prepared from (1S,4S)-2-[4-(3-piperidin-1-ylpropoxy)benzoyl]-2,5-diaza-bicyclo[2.2.1] heptane dihydrochloride (D9) and the appropriate carbamoyl chloride following the procedure described for Example 59, and displayed ^{1}H NMR and mass spectral data that were consistent with structure.



Example No	R^x	Mass Spectrum (ES^+)
E80		$[M+H]^+$ 441
E81		$[M+H]^+$ 457

Examples 82-87 (E82-E87)

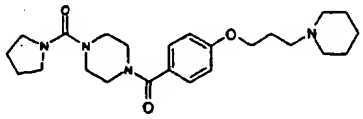
Examples 82-87 were prepared from 1-[4-(3-piperidin-1-ylpropoxy)benzoyl]piperazine dihydrochloride (D5) and the appropriate carboxylic acid chloride using the procedure described in Example 59 and displayed ^{1}H NMR and mass spectral data that were consistent with structure.



Example No	R^x	Mass Spectrum (ES^+)
E82		$[M+H]^+$ 402
E83		$[M+H]^+$ 436
E84		$[M+H]^+$ 471
E85		$[M+H]^+$ 471
E86		$[M+H]^+$ 504
E87		$[M+H]^+$ 504

Example 88

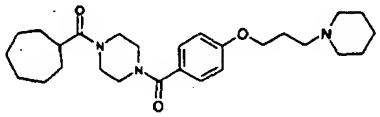
1-[4-(3-Piperidin-1-ylpropoxy)benzoyl]-4-(pyrrolidine-1-carbonyl)-piperazine hydrochloride (E88)



The title compound (E88) was prepared from 1-[4-(3-piperidin-1-ylpropoxy)benzoyl]piperazine dihydrochloride) (D5) (0.15g) and pyrrolidine-1-carbonyl chloride (0.054 g) using the procedure described in Example 59 and was obtained as a white solid (0.10 g). MS electrospray (+ion) 429 (MH^+). ^1H NMR δ (DMSO-d6): 9.75 (s, 1H), 7.40 (d, 2H, J=8.4Hz), 7.00 (d, 2H, J=8.4 Hz), 4.10 (t, 2H, J=6.0Hz), 3.47 (m, 6H), 3.27 (m, 4H), 3.18 (m, 6H), 2.87 (m, 2H), 2.17 (m, 2H), 1.74-1.39 (m, 10H).

Example 89

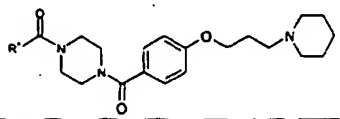
1-[4-(3-Piperidin-1-ylpropoxy)benzoyl]-4-(cycloheptanecarbonyl)-piperazine hydrochloride (E89)



1-[4-(3-Piperidin-1-ylpropoxy)benzoyl]piperazine dihydrochloride (D5) (0.15g) was dissolved in DCM (5ml) and diethylaminomethyl polystyrene resin (3.2 mmol/g, 0.465 g) was added, followed by cycloheptane carboxylic acid (0.063g) , HOBT (0.065 g), and EDC (0.092g). The reaction was stirred at rt overnight, then filtered and washed with saturated sodium hydrogen carbonate solution (3x50ml) and brine (50ml). The organic layer was dried (magnesium sulphate) and evaporated to give a crude product, which was purified by column chromatography [silica gel, eluted with 0-10% MeOH (containing 10% 0.880 ammonia solution) in DCM]. The isolated free base was then dissolved in DCM (5ml) and treated with 4N HCl/dioxane solution (1ml) and stirred for 10min. The reaction was concentrated, and the residue co-evaporated with toluene (3x10ml) then dried at 50°C under high vacuum for 16h to yield the title compound (E89) as a pale solid (0.051g). MS electrospray (+ion) 456 (MH^+).^1H NMR δ (DMSO-d6): 9.55 (s, 1H), 7.40 (d, 2H, J=8.76 Hz), 7.00 (d, 2H, J=8.76Hz), 4.10 (t, 2H, J=9.93 Hz), 3.51 (m, 10H), 3.17 (m, 2H), 2.90 (m, 2H), 2.73 (m, 1H), 2.18 (m, 2H), 1.83-1.66 (m, 9H), 1.44 (m, 9H).

Examples 90-99 (E90-E99)

Examples 90-99 were prepared from 1-[4-(3-piperidin-1-ylpropoxy)benzoyl]piperazine dihydrochloride (D5) and the appropriate carboxylic acid using the procedure described in Example 89 and displayed ^1H NMR and mass spectral data that were consistent with structure.

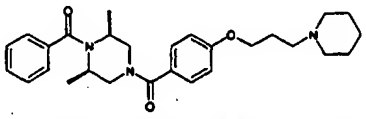


Example No	R^x	Mass Spectrum (ES^+)
E90		$[M+H]^+$ 437
E91		$[M+H]^+$ 451

E92		$[M+H]^+$ 452
E93		$[M+H]^+$ 456
E94		$[M+H]^+$ 498
E95		$[M+H]^+$ 430
E96		$[M+H]^+$ 444
E97		$[M+H]^+$ 464
E98		$[M+H]^+$ 490
E99		$[M+H]^+$ 478

Example 100

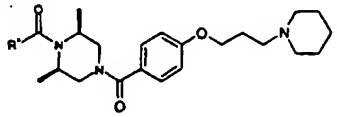
(3R,5S)-1-[4-(3-Piperidin-1-ylpropoxy)benzoyl]-3,5-dimethyl-4-benzoyl-piperazine] hydrochloride (E100)



(3R,5S)-1-[4-(3-Piperidin-1-ylpropoxy)benzoyl]-3,5-dimethylpiperazine (D10) (0.15g) was dissolved in DCM (5ml) and treated with diethylaminomethyl polystyrene resin (3.2mmol/g, 0.60g) followed by benzoyl chloride (0.053g). The reaction was stirred at rt for 16h and then loaded directly onto a silica column, eluting with 0-10% MeOH (containing 10% 0.880 ammonia solution)/DCM. The isolated free base product was then dissolved in DCM (5ml) and treated with 4N HCl/Dioxane solution (1ml) and stirred for 10min. The reaction was concentrated, and the residue co-evaporated with toluene (3x10ml) then dried at 50°C under high vacuum for 16h to yield the title compound (E100) as a white solid (0.10g). MS electrospray (+ion) 464 (MH^+). ^1H NMR δ (DMSO-d6): 9.74 (1H, s), 7.39 (7H, m), 7.01 (2H, d, J=8.7Hz), 4.40-4.09 (4H, m) 3.47-3.15 (6H, m), 2.92 (2H, m), 2.20-1.28 (10H, m), 1.15 (6H, m).

Examples 101-102 (E101-E102)

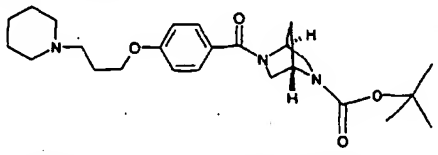
Examples 101-102 were prepared from (3R,5S)-1-[4-(3-piperidin-1-ylpropoxy)benzoyl]-3,5-dimethylpiperazine (D10) and the appropriate carboxylic acid chloride using the procedure described in Example 100 and displayed ^1H NMR and mass spectral data that were consistent with structure.



Example No	R^x	Mass Spectrum (ES^+)
E101		$[M+H]^+$ 454
E102		$[M+H]^+$ 470

Example 103

(1S,4S)-5-[4-(3-Piperidin-1-ylpropoxy)benzoyl]-2,5-diaza-bicyclo[2.2.1] heptane-2 carboxylic acid t-butyl ester (E103)



To (1S,4S)-2,5-diaza-bicyclo[2.2.1]heptane-2-carboxylic acid t-butyl ester (1.12g) in DCM (10ml) was added triethylamine (1.77ml) and the reaction was cooled to 0°C followed by the slow addition of 4-(3-piperidin-1-ylpropoxy)benzoyl chloride hydrochloride (D3) (1.8g) in DCM (10ml). The mixture was stirred at rt for 3h, then washed with water. The organic layer was dried ($MgSO_4$) and evaporated to give the title compound (E103) as a cream coloured solid (2.52g).
Mass Spectrum 444 $[M+H]^+$

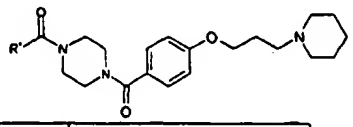
Example 104

(1S,4S)-2-[4-(3-Piperidin-1-ylpropoxy)benzoyl]-2,5-diaza-bicyclo[2.2.1]heptane dihydrochloride (E104)

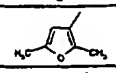
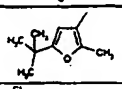
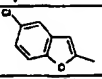
To (1S,4S)-5-[4-(3-piperidin-1-ylpropoxy)benzoyl]-2,5-diaza-bicyclo[2.2.1] heptane-2 carboxylic acid tert-butyl ester (E103) (2.52g) in DCM (30ml) was added 4N HCl (5ml) and the mixture was allowed to stir at rt overnight. Evaporation of solvent followed by drying under high vacuum afforded the title compound (E104) as a foam (1.2g).

Examples 105-114 (E105-E114)

Examples 105 - 114 were prepared from 1-[4-(3-piperidin-1-ylpropoxy)benzoyl]piperazine dihydrochloride (D5) and the appropriate acid using a similar procedure to that described in Example 89 and employing either DCM or DMF as solvent. All compounds displayed ^1H NMR and mass spectral data that were consistent with structure.



Example No	R^x	Mass Spectrum (ES^+)
E105		$[M+H]^+$ 338

E106		$[M+H]^+$ 430
E107		$[M+H]^+$ 476
E108		$[M+H]^+$ 494
E109		$[M+H]^+$ 426
E110		$[M+H]^+$ 454
E111		$[M+H]^+$ 496
E112		$[M+H]^+$ 511/513
E113		$[M+H]^+$ 490
E114		$[M+H]^+$ 445

Examples 115-122 (E115-E122)

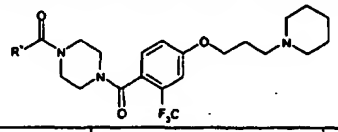
Examples 115-122 were prepared using either Method A or B according to the table, and displayed ^1H NMR and mass spectral data that were consistent with structure.

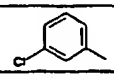
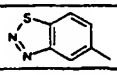
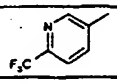
Method A

1-[4-(3-Piperidin-1-ylpropoxy)-2-trifluoromethyl-benzoyl]piperazine dihydrochloride (D25) was reacted with the appropriate acid chloride following the method of Example 100 (E100). The isolated free base was converted into the hydrochloride salt and crystallised from acetone.

Method B

1-[4-(3-Piperidin-1-ylpropoxy)-2-trifluoromethyl-benzoyl]piperazine dihydrochloride (D25) was reacted with the appropriate carboxylic acid following the method of Example 89 (E89) except that DMF was employed as solvent. The isolated free base was converted into the hydrochloride salt and crystallised from acetone.

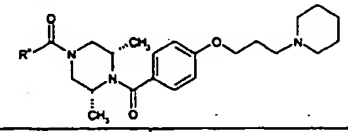


Example No	R^x	Mass Spectrum (ES^+)	Synthetic Method
E115		$[M+H]^+$ 494	A
E116		$[M+H]^+$ 510	A
E117		$[M+H]^+$ 539	A
E118		$[M+H]^+$ 497	A
E119		$[M+H]^+$ 562	B
E120		$[M+H]^+$ 573	B

E121		$[M+H]^+$ 498	B
E122		$[M+H]^+$ 512	B

Examples 123 and 124 (E123-E124)

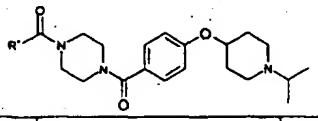
Examples 123 and 124 were prepared from (2*R*,6*S*)-2,6-dimethyl-1-[4-(3-piperidin-1-yl)propoxybenzoyl]piperazine dihydrochloride (D28) and the appropriate acid chloride using the method of Example 59 and displayed ^{1}H NMR and mass spectral data that were consistent with structure.



Example No	R^x	Mass Spectrum (ES^+)
E123		$[M+H]^+$ 454
E124		$[M+H]^+$ 470

Examples 125-127 (E125-E127)

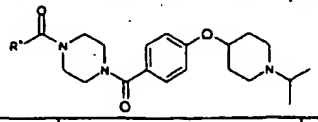
Examples 125-127 were prepared from 4-[(1-isopropyl-4-piperidinyl)oxy]benzoyl] piperazine dihydrochloride (D38) and the appropriate acid chloride using the method of Example 59 and displayed ^{1}H NMR and mass spectral data that were consistent with structure.



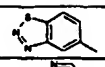
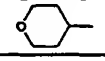
Example No	R^x	Mass Spectrum (ES^+)
E125		$[M+H]^+$ 442
E126		$[M+H]^+$ 426
E127		$[M+H]^+$ 471/473

Examples 128-131 (E128-E131)

Examples 128-131 were prepared from 4-[(1-isopropyl-4-piperidinyl)oxy]benzoyl] piperazine dihydrochloride (D38) and the appropriate acid using the method of Example 89 and displayed ^{1}H NMR and mass spectral data that were consistent with structure.

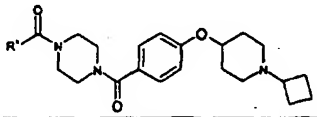


Example No	R^x	Mass Spectrum (ES^+)

E128		$[M+H]^+$ 494
E129		$[M+H]^+$ 505
E130		$[M+H]^+$ 430
E131		$[M+H]^+$ 444

Examples 132-134 (E132-E134)

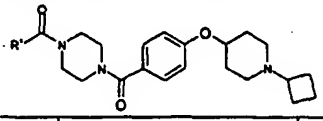
Examples 132-134 were prepared from 4-[(1-cyclobutyl-4-piperidinyl)oxy]benzoyl] piperazine dihydrochloride (D37) and the appropriate acid chloride using the method of Example 59 and displayed ^1H NMR and mass spectral data that were consistent with structure.

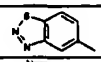


Example No	R^X	Mass Spectrum (ES^+)
E132		$[M+H]^+$ 454
E133		$[M+H]^+$ 438
E134		$[M+H]^+$ 483/485

Examples 135-138 (E135-E138)

Examples 135-138 were prepared from from 4-[(1-cyclobutyl-4-piperidinyl)oxy]benzoyl] piperazine dihydrochloride (D37) and the appropriate acid using the method of Example 89 except that DMF was used as solvent and displayed ^1H NMR and mass spectral data that were consistent with structure.

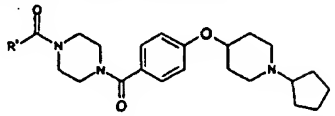


Example No	R^X	Mass Spectrum (ES^+)
E135		$[M+H]^+$ 506
E136		$[M+H]^+$ 517
E137		$[M+H]^+$ 442
E138		$[M+H]^+$ 456

Examples 139-142 (E139-E142)

Examples 139-142 were prepared from 4-[(1-cyclopentyl-4-piperidinyl)oxy]benzoyl]piperazine dihydrochloride (D39) and the appropriate acid

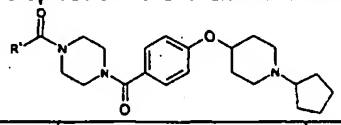
chloride using the method of Example 59 and displayed ^{1}H NMR and mass spectral data that were consistent with structure.

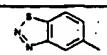
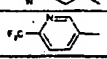


Example No	R^X	Mass Spectrum (ES^+)
E139		$[M+H]^+$ 468
E140		$[M+H]^+$ 452
E141		$[M+H]^+$ 497/499
E142		$[M+H]^+$ 455

Examples 143-146 (E143-146)

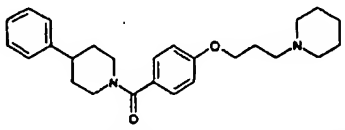
Examples 143-146 were prepared from from 4-[(1-cyclopentyl-4-piperidinyl)oxy]benzoyl]piperazine dihydrochloride (D39) and the appropriate acid using the method of of Example 89 except that DMF was used as solvent and displayed ^{1}H NMR and mass spectral data that were consistent with structure.



Example No	R^X	Mass Spectrum (ES^+)
E143		$[M+H]^+$ 520
E144		$[M+H]^+$ 531
E145		$[M+H]^+$ 456
E146		$[M+H]^+$ 470

Example 147

N-[4-(3-Piperidin-1-ylpropoxy)benzoyl]-4-phenylpiperidine hydrochloride (E147)

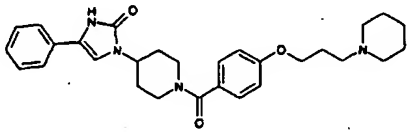


A solution of 4-(3-piperidin-1-ylpropoxy)benzoic acid hydrochloride (D2)(150mg) in thionyl chloride (2ml) was refluxed for 1h, cooled to rt and evaporated. The acid chloride was re-evaporated from DCM (2x3ml). The residue was redissolved in DCM (5ml) and triethylamine (0.21ml) and added to a stirred solution of 4-phenylpiperidine (81mg) in DCM (2ml) at rt. The mixture was stirred for 1h and then chromatographed (silica gel, step gradient 4-8% MeOH in DCM). Fractions containing the required product were treated with excess hydrogen chloride (4M solution in dioxan) and then concentrated to

yield the title compound (E147) (173mg). MS electrospray (+ion) 407 (MH^+). ^1H NMR δ (DMSO-d6): 10.29 (1H, s), 7.41 (2H, d, J=8.5Hz), 7.28 (5H, m), 6.99 (2H, d, J=8.5Hz), 4.10 (2H, t, J=6.5Hz), 2.70-3.53 (11H, m), 2.24 (2H, m), 1.30-1.85 (10H, m).

Example 148

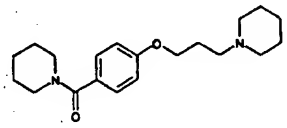
N-[4-(3-Piperidin-1-ylpropoxy)benzoyl]-4-(4-phenyl-1,3-dihydroimidazol-2-one-1-yl)piperidine hydrochloride (E148)



4-(3-Piperidin-1-ylpropoxy)benzoic acid hydrochloride (D2) (49mg) was converted to the title compound (E148) by reaction with 4-phenyl-1,3-dihydroimidazol-2-one-1-ylpiperidine (Carling *et al.*, J. Med. Chem., 1999, **42**, 2706) (40mg) using the method described in Example 1 (E1) (yield = 73mg). MS electrospray (+ion) 490 (MH^+). ^1H NMR δ (DMSO-d6): 10.73 (1H, s), 9.58 (1H, s), 6.96-7.55 (10H, m), 4.14 (2H, t, J=6Hz), 3.25-3.77 (9H, m), 2.90 (2H, m), 2.17 (2H, m), 1.13-1.89 (10H, m).

Example 149

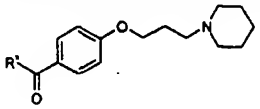
N-[4-(3-Piperidin-1-ylpropoxy)benzoyl]piperidine hydrochloride (E149)



A solution of 4-(3-piperidin-1-ylpropoxy)benzoic acid hydrochloride (D2) (227mg) in DMF at rt was treated with Argonaut PS Carbodiimide resin (778mg, 1.3mmol/g) and stirred for 5min. Piperidine (0.05ml) was added and the mixture stirred overnight, filtered and evaporated. The residue was partitioned between EtOAc (10ml) and saturated sodium hydrogen carbonate solution (5ml). The organic phase was collected, washed with water (3x), saturated brine, dried ($MgSO_4$) treated with excess hydrogen chloride (4M in dioxan) and evaporated to yield the title compound (E149) (72mg). MS electrospray (+ion) 331 (MH^+). ^1H NMR δ (DMSO-d6): 10.30 (1H, s), 7.33 (2H,d,J=8.8Hz), 6.97 (2H,d,J=8.8Hz), 4.10 (2H, t, J=6Hz), 2.75-3.70 (10H, m), 2.20 (2H, m), 1.25-1.91 (12H, m).

Examples 150-151 (E150-151)

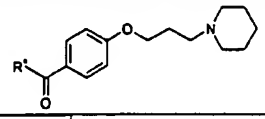
Examples 150-151 were prepared from 4-(3-piperidin-1-ylpropoxy)benzoic acid hydrochloride (D2) and the appropriate amine using the method outlined in Example 147 (E1) and displayed ^1H NMR and mass spectral data that were consistent with structure.

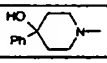


Example No	R^x	Mass Spectrum (ES^+)
E150		345 $[M+H]^+$
E151		359 $[M+H]^+$

Example 152 (E152)

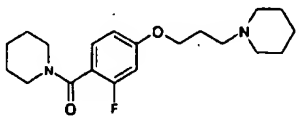
Example 152 was prepared from 4-(3-piperidin-1-ylpropoxy)benzoic acid hydrochloride (D2) and 4-hydroxy-4-phenylpiperidine using the method outlined in Example 147 (E147) with the exception that polymer supported base was employed. ^1H NMR and mass spectral data were consistent with structure.



Example No	R^x	Mass Spectrum
E152		423 $[M+H]^+$

Example 153

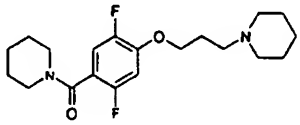
N-[2-Fluoro-4-(3-piperidin-1-ylpropoxy)benzoyl]piperidine hydrochloride (E153)



The title compound (E153) was prepared from 2-fluoro-4-(3-piperidin-1-ylpropoxy)benzoyl chloride hydrochloride (D22) and piperidine using the method described in Example 59. MS electrospray (+ion) 349 (MH^+)

Example 154

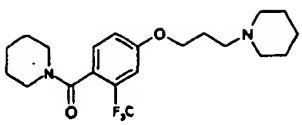
N-[2,5-Difluoro-4-(3-piperidin-1-ylpropoxy)benzoyl]piperidine hydrochloride (E154)



The tile compound (E154) was prepared from 2,5-difluoro-4-(3-piperidin-1-ylpropoxy)benzoyl chloride hydrochloride (D19) and piperidine using the method described in Example 59. MS electrospray (+ion) 367 (MH^+)

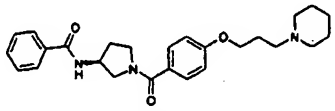
Example 155

N-[2-Trifluoromethyl-4-(3-Piperidin-1-ylpropoxy)benzoyl]piperidine hydrochloride (E155)



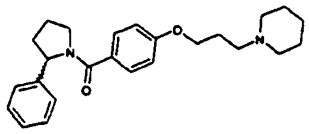
The tile compound (E155) was prepared from 4-(3-piperidin-1-yl-propoxy)-2-trifluoromethyl-benzoyl chloride hydrochloride (D16) and piperidine using the method described in Example 59. MS electrospray (+ion) 399 (MH^+)

Example 156
(S)-N-[4-(3-Piperidin-1-ylpropoxy)benzoyl]-3-benzamidopyrrolidine dihydrochloride (E156)



A stirred solution of (S)-N-[4-(3-piperidin-1-ylpropoxy)benzoyl]-3-aminopyrrolidine dihydrochloride (D11) (134mg) and triethylamine (0.18ml) in DCM at rt was treated with benzoyl chloride (0.046ml). After 2h the mixture was washed with saturated sodium hydrogen carbonate solution (5ml), water (3x5ml), dried ($MgSO_4$) and evaporated. The residue was chromatographed (silica gel, step gradient 0-20% MeOH in DCM). Fractions containing the required product were treated with excess hydrogen chloride (4M solution in dioxan) and then concentrated to yield the title compound (E156) (56mg). MS electrospray (+ion) 436 (MH^+). ^1H NMR δ (DMSO-d6) at 353 °K: 10.15 (1H,s), 8.30 (1H,d,J=5.5Hz), 7.82 (2H,d,J=8Hz), 7.45 (5H,m), 6.97 (2H,d,J=8Hz), 4.45 (1H,m), 4.12 (2H,t,J=6Hz), 3.68 (2H,s), 2.80-3.90 (11H, m), 2.90 (2H,m), 2.18 (2H,m), 1.38-2.35 (6H,m).

Example 157
N-[4-(3-Piperidin-1-ylpropoxy)benzoyl]-(R,S)-2-phenylpyrrolidine hydrochloride (E157)

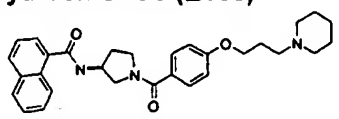


A solution of 4-(3-piperidin-1-ylpropoxy)benzoic acid hydrochloride (D2) (299mg) in thionyl chloride (8ml) was refluxed for 1h, cooled to rt and evaporated. The acid chloride was re-evaporated from DCM (2x5ml). The residue was redissolved in DCM (15ml) and triethylamine (0.43ml) and added to a stirred solution of (R,S)-2-phenylpyrrolidine (147mg) in DCM (5ml) at rt. The mixture was stirred for 1h, washed with saturated sodium hydrogen carbonate solution (10ml), water (3x10ml), dried ($MgSO_4$) and evaporated. The residue was chromatographed (silica gel, step gradient 2-7% MeOH (containing 10% .880 ammonia solution) in DCM). Fractions containing the required product were treated with excess hydrogen chloride (4M solution in dioxan) and then

concentrated to yield the title compound (E157) (332mg). MS electrospray (+ion) 393 (MH^+). ^1H NMR δ (DMSO-d6): at 353 ° K 10.20 (1H, s), 7.40 (2H, d, J=8.5Hz), 7.25 (5H, m), 6.89(2H, d, J=8.5Hz), 5.11 (1H, m), 4.09 (2H, t, J=6.5Hz), 2.80-3.83 (6H, m), 2.05-2.55 (6H, m), 1.31-1.93 (8H, m).

Example 158

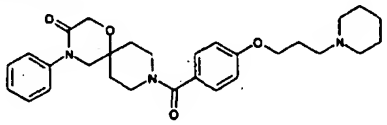
(S)-N-[4-(3-Piperidin-1-ylpropoxy)benzoyl]-3-(naphthalene-1-carboxamidopyrrolidine dihydrochloride (E158)



The title compound (E158) was prepared from (S)-N-[4-(3-piperidin-1-ylpropoxy)benzoyl]-3-aminopyrrolidine dihydrochloride (D11) and 1-naphthoyl chloride using the method outlined in Example 156. MS electrospray (+ion) 486 (MH^+). ^1H NMR data consistent with structure.

Example 159

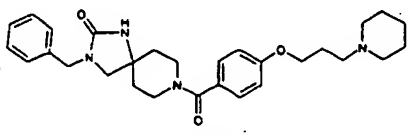
4-Phenyl-9-[4-(3-piperidin-1-ylpropoxy)benzoyl]-1-oxa-4,9-diazaspiro-[5,5]-undecan-3-one hydrochloride (E159)



A solution of 4-(3-piperidin-1-ylpropoxy)benzoic acid hydrochloride (D2) (97mg) in thionyl chloride (2.6ml) was refluxed for 1h, cooled to rt and evaporated. The acid chloride was re-evaporated from DCM (2x3ml). The residue was redissolved in DCM (5ml) and triethylamine (0.14ml) and added to a stirred solution of 4-phenyl-1-oxa-4,9-diazaspiro-[5,5]-undecan-3-one (80mg) (Caroon *et al.*, J. Med. Chem., 1981, **24**, 1320) in DCM (2ml) at rt. The mixture was stirred for 1h, washed with saturated sodium hydrogen carbonate solution (5ml), water (3x5ml), dried ($MgSO_4$) and evaporated. The residue was chromatographed [silica gel, step gradient 0-5% MeOH (containing 10% of .880 ammonia solution) in DCM]. Fractions containing the required product were treated with excess hydrogen chloride (4M solution in dioxan) and then concentrated to yield the title compound (E159) (79mg). MS electrospray (+ion) 492 (MH^+). ^1H NMR δ (DMSO-d6): 9.77 (1H, s), 6.98-7.44 (9H, m), 4.25 (2H, s), 4.10 (2H, t, J=6Hz), 3.68 (2H, s), 3.05-3.78 (8H, m), 2.90 (2H, m), 2.18 (2H, m), 1.28-2.05 (10H, m).

Example 160

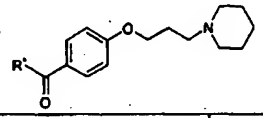
3-Benzyl-8-[4-(3-piperidin-1-ylpropoxy)benzoyl]-1,3,8-triaza-spiro[4.5]-decan-2-one (E160)

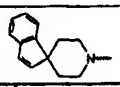
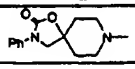


4-(3-Piperidin-1-ylpropoxy)benzoic acid hydrochloride (D2) (49mg) was converted to the title compound (E160) by reaction with 3-benzyl-1,3,8-triaza-spiro[4.5]decan-2-one (Smith *et al.*, J. Med. Chem., 1995, **38**, 3772) (40mg) using the method described in Example 159 (E159) with the exception that the product was isolated as the free base. (yield = 47mg). MS electrospray (+ion) 491 (MH^+). ^1H NMR δ ($CDCl_3$): 6.86-7.42 (9H, m), 4.88 (1H, s), 4.39 (2H, s), 4.00 (2H, t, J=6.4Hz), 3.65 (4H, m), 3.14 (2H, s), 2.45 (2H, m), 1.98 (2H, m), 1.37-1.82 (10H, m).

Examples 161-162 (E161-162)

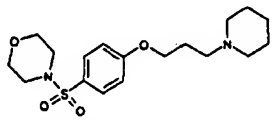
Examples 161-162 were prepared from 4-(3-piperidin-1-ylpropoxy)benzoic acid hydrochloride (D2) and the appropriate amine using the method outlined in Example 159 (E159) and displayed ^1H NMR and mass spectral data that were consistent with structure.



Example No	R^x	Mass Spectrum (ES^+)
E161		431 $[M+H]^+$
E162		478 $[M+H]^+$

Example 163

N-[4-(3-Piperidin-1-ylpropoxy)benzenesulfonyl]morpholine hydrochloride (E163)

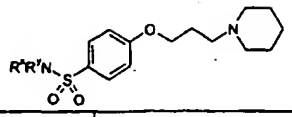


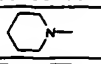
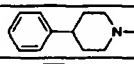
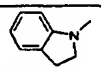
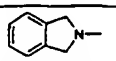
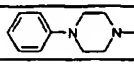
A solution of 4-[4-(3-bromopropoxy)benzenesulfonyl]morpholine (D13) (96mg) in 1-butanol (5ml) and piperidine (0.22ml) was heated at 100°C for 16h, cooled to rt and evaporated. The residue was redissolved in EtOAc (10ml), washed with saturated sodium hydrogen carbonate solution (5ml), water (3x5ml), dried ($MgSO_4$) and evaporated. The residue was redissolved in DCM and treated with excess hydrogen chloride (4M solution in dioxan) and then concentrated to yield the title compound (E163) (75mg). MS electrospray (+ion) 369 (MH^+). ^1H NMR δ (DMSO-d6): 10.21 (1H, s), 7.68 (2H, d, J=8.8Hz), 7.18 (2H, d, J=8.8Hz), 4.18 (2H, t, J=6Hz), 3.62 (2H, m), 3.44 (2H, m), 3.17 (2H, m), 2.84 (6H, m), 1.30-1.85 (6H, m).

Examples 164-168 (E164-168)

Examples 164-168 were prepared from the appropriate amine using an analogous method to that described in Description 13 (D13) followed by Example 163 (E163). All

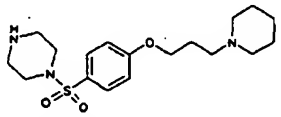
compounds displayed ^1H NMR and mass spectral data that were consistent with structure.



Example No	R^XR^YN	Mass Spectrum
E164		367 $[M+H]^+$
E165		443 $[M+H]^+$
E166		401 $[M+H]^+$
E167		401 $[M+H]^+$
E168		444 $[M+H]^+$

Example 169

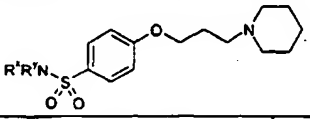
N-[4-(3-Piperidin-1-ylpropoxy)benzenesulfonyl]piperazine dihydrochloride (E169)

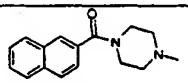
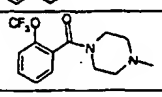


The title compound (E169) was prepared using an analogous method to that described in Description 13 (D13) followed by Example 163 (E163) by treating N-Boc piperazine with 1-bromo-3-(4-chlorosulfonylphenoxy)propane followed by reaction with piperidine. Subsequent deprotection with HCl afforded the dihydrochloride salt. MS electrospray (+ion) 368 (MH^+).

Examples 170-171 (E170-171)

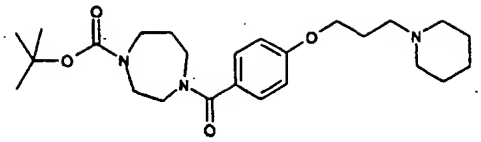
Examples 170-171 were prepared from Example 169 (E169) by treatment with the appropriate acid chloride in the presence of triethylamine using DCM as solvent.



Example No	R^XR^YN	Mass Spectrum
E170		522 $[M+H]^+$
E171		556 $[M+H]^+$

Example 172

1-[4-(3-Piperidin-1-ylpropoxy)benzoyl]-4-t-butoxycarbonylhomopiperazine (E172)



To t-butoxycarbonylhomopiperazine (0.76g) in DCM (10ml) was added triethylamine (1.2ml) and the mixture was cooled to 0°C followed by the slow addition of 4-(3-piperidin-1-ylpropoxy)benzoyl chloride hydrochloride (D3) (1.2g) in DCM (10ml). The mixture was stirred at rt for 3h, then washed with water. The organic layer was dried ($MgSO_4$) and evaporated to give the title compound (E172) as a cream coloured solid (1.69g).
Mass Spectrum 446 $[M+H]^+$

Abbreviations

Boc	tertbutoxycarbonyl
EtOAc	ethyl acetate
h	hour
DCM	dichloromethane
MeOH	methanol
rt	room temperature
DCC	dicyclohexylcarbodiimide
DMF	dimethylformamide

All publications, including but not limited to patents and patent applications, cited in this specification are herein incorporated by reference as if each individual publication were specifically and individually indicated to be incorporated by reference herein as though fully set forth.

Biological Data

A membrane preparation containing histamine H3 receptors may be prepared in accordance with the following procedures:

(i) Generation of histamine H3 cell line

DNA encoding the human histamine H3 gene (Huvar, A. *et al.* (1999) Mol. Pharmacol. **55(6)**, 1101-1107) was cloned into a holding vector, pCDNA3.1 TOPO (InVitrogen) and its cDNA was isolated from this vector by restriction digestion of plasmid DNA with the enzymes BamH1 and Not-1 and ligated into the inducible expression vector pGene (InVitrogen) digested with the same enzymes. The GeneSwitch™ system (a system where in transgene expression is switched off in the absence of an inducer and switched on in the presence of an inducer) was performed as described in US Patent nos: 5,364,791; 5,874,534; and 5,935,934. Ligated DNA was transformed into competent DH5α E. coli host bacterial cells and plated onto Luria Broth (LB) agar containing Zeocin™ (an antibiotic which allows the selection of cells expressing the sh ble gene

which is present on pGene and pSwitch) at 50μg ml^{-1}. Colonies containing the re-ligated plasmid were identified by restriction analysis. DNA for transfection into mammalian cells was prepared from 250ml cultures of the host bacterium containing the pGeneH3 plasmid and isolated using a DNA preparation kit (Qiagen Midi-Prep) as per manufacturers guidelines (Qiagen).

CHO K1 cells previously transfected with the pSwitch regulatory plasmid (InVitrogen) were seeded at 2x10e6 cells per T75 flask in Complete Medium, containing Hams F12 (GIBCOBRL, Life Technologies) medium supplemented with 10% v/v dialysed foetal bovine serum, L-glutamine, and hygromycin (100μg ml^{-1}), 24 hours prior to use. Plasmid DNA was transfected into the cells using Lipofectamine plus according to the manufacturers guidelines (InVitrogen). 48 hours post transfection cells were placed into complete medium supplemented with 500μg ml^{-1} Zeocin™.

10-14 days post selection 10nM Mifepristone (InVitrogen), was added to the culture medium to induce the expression of the receptor. 18 hours post induction cells were detached from the flask using ethylenediamine tetra-acetic acid (EDTA; 1:5000; InVitrogen), following several washes with phosphate buffered saline pH 7.4 and resuspended in Sorting Medium containing Minimum Essential Medium (MEM), without phenol red, and supplemented with Earles salts and 3% Foetal Clone II (Hyclone). Approximately 1x 10e7 cells were examined for receptor expression by staining with a rabbit polyclonal antibody, 4a, raised against the N-terminal domain of the histamine H3 receptor, incubated on ice for 60 minutes, followed by two washes in sorting medium. Receptor bound antibody was detected by incubation of the cells for 60 minutes on ice with a goat anti rabbit antibody, conjugated with Alexa 488 fluorescence marker (Molecular Probes). Following two further washes with Sorting Medium, cells were filtered through a 50μm Filcon™ (BD Biosciences) and then analysed on a FACS Vantage SE Flow Cytometer fitted with an Automatic Cell Deposition Unit. Control cells were non-induced cells treated in a similar manner. Positively stained cells were sorted as single cells into 96-well plates, containing Complete Medium containing 500μg ml^{-1} Zeocin™ and allowed to expand before reanalysis for receptor expression via antibody and ligand binding studies. One clone, 3H3, was selected for membrane preparation.

(ii) Membrane preparation from cultured cells

All steps of the protocol are carried out at 4°C and with pre-cooled reagents. The cell pellet is resuspended in 10 volumes of buffer A2 containing 50mM N-2-hydroxyethylpiperazine-N'-2-ethanesulfonic acid (HEPES) (pH 7.40) supplemented with 10e-4M leupeptin (acetyl-leucyl-leucyl-arginal; Sigma L2884), 25μg/ml bacitracin (Sigma B0125), 1mM ethylenediamine tetra-acetic acid (EDTA), 1mM phenylmethylsulfonyl fluoride (PMSF) and 2x10e-6M pepstain A (Sigma). The cells are then homogenised by 2 x 15 second bursts in a 1 litre glass Waring blender, followed by centrifugation at 500g for 20 minutes. The supernatant is then spun at 48,000g for 30 minutes. The pellet is resuspended in 4 volumes of buffer A2 by vortexing for 5 seconds, followed by

homogenisation in a Dounce homogeniser (10-15 strokes). At this point the preparation is aliquoted into polypropylene tubes and stored at -70°C.

Compounds of the invention may be tested for in vitro biological activity in accordance with the following assays:

(I) Histamine H3 binding assay

For each compound being assayed, in a white walled clear bottom 96 well plate, is added:-

(a) 10µl of test compound (or 10µl of iodophenpropit (a known histamine H3 antagonist) at a final concentration of 10mM) diluted to the required concentration in 10% DMSO;

(b) 10µl ^{125}I 4-[3-(4-iodophenylmethoxy)propyl]-1H-imidazolium (iodoproxyfan) (Amersham; 1.85MBq/µl or 50µCi/ml; Specific Activity ~2000Ci/mmol) diluted to 200pM in assay buffer (50mM Tris(hydroxymethyl)aminomethane buffer (TRIS) pH 7.4, 0.5mM ethylenediamine tetra-acetic acid (EDTA)) to give 20pM final concentration; and

(c) 80µl bead/membrane mix prepared by suspending Scintillation Proximity Assay (SPA) bead type WGA-PVT at 100mg/ml in assay buffer followed by mixing with membrane (prepared in accordance with the methodology described above) and diluting in assay buffer to give a final volume of 80µl which contains 7.5µg protein and 0.25mg bead per well – mixture was pre-mixed at room temperature for 60 minutes on a roller. The plate is shaken for 5 minutes and then allowed to stand at room temperature for 3-4 hours prior to reading in a Wallac Microbeta counter on a 1 minute normalised tritium count protocol. Data was analysed using a 4-parameter logistic equation.

(II) Histamine H3 functional antagonist assay

For each compound being assayed, in a white walled clear bottom 96 well plate, is added:-

(a) 10µl of test compound (or 10µl of guanosine 5'- triphosphate (GTP) (Sigma) as non-specific binding control) diluted to required concentration in assay buffer (20mM N-2-Hydroxyethylpiperazine-N'-2-ethanesulfonic acid (HEPES) + 100mM NaCl + 10mM $MgCl_2$, pH7.4 NaOH);

(b) 60µl bead/membrane/GDP mix prepared by suspending wheat germ agglutinin-polyvinyltoluene (WGA-PVT) scintillation proximity assay (SPA) beads at 100mg/ml in assay buffer followed by mixing with membrane (prepared in accordance with the methodology described above) and diluting in assay buffer to give a final volume of 60µl which contains 10µg protein and 0.5mg bead per well – mixture is pre-mixed at 4°C for 30 minutes on a roller and just prior to addition to the plate, 10µM final concentration of guanosine 5' diphosphate (GDP) (Sigma; diluted in assay buffer) is added;

The plate is incubated at room temperature to equilibrate antagonist with receptor/beads by shaking for 30 minutes followed by addition of:

(c) 10µl histamine (Tocris) at a final concentration of 0.3µM; and

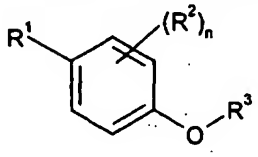
(d) 20µl guanosine 5' [γ35-S] thiotriphosphate, triethylamine salt (Amersham; radioactivity concentration = 37kBq/µl or 1mCi/ml; Specific Activity 1160Ci/mmol) diluted to 1.9nM in assay buffer to give 0.38nM final.
The plate is then incubated on a shaker at room temperature for 30 minutes followed by centrifugation for 5 minutes at 1500 rpm. The plate is read between 3 and 6 hours after completion of centrifuge run in a Wallac Microbeta counter on a 1 minute normalised tritium count protocol. Data is analysed using a 4-parameter logistic equation. Basal activity used as minimum i.e. histamine not added to well.

Results

The compounds of Examples E1-E103 and E105-E172 were tested in the histamine H3 functional antagonist assay and exhibited pK_b values >7.5. More particularly, the compounds of Examples E1-3, E5-7, E9, E11, E13-16, E18-19, E21-25, E28, E30, E33, E35, E37-41, E47, E49, E51-53, E57, E59-61, E63-65, E67-68, E72, E75, E78, E80, E84-86, E88-89, E93-94, E96, E98, E99-E101, E107-108, E110-111, E115-119, E121-122, E123, E125, E128-131, E132-138, E139-146, E149-151, E155-160, E162, E164-165, E170 exhibited pK_b values >8.5.

CLAIMS:

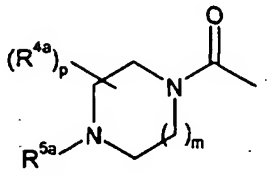
1. A compound of formula (I) or a pharmaceutically acceptable salt thereof:



(I)

wherein:

R^1 represents a group of formula (A):



(A)

wherein R^{4a} represents C_{1-6} alkyl, oxo, aryl, heteroaryl or heterocyclyl;

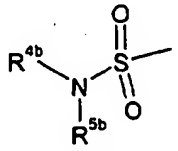
R^{5a} represents hydrogen, -C_{1-6} alkyl, -C_{1-6} alkylC_{1-6} alkoxy, -C_{1-6} alkoxycarbonyl, -C_{3-8} cycloalkyl, -aryl, -heterocyclyl, heteroaryl, -C_{1-6} alkyl-aryl, -CH(aryl)(aryl), -C_{1-6} alkyl-C_{3-8} cycloalkyl, -C_{1-6} alkyl-heteroaryl or -C_{1-6} alkyl-heterocyclyl,

wherein R^{5a} may be optionally substituted by one or more substituents which may be the same or different, and which are selected from the group consisting of halogen, hydroxy, cyano, nitro, oxo, haloC_{1-6} alkyl, polyhaloC_{1-6} alkyl, haloC_{1-6} alkoxy, polyhaloC_{1-6} alkoxy, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} alkylthio, C_{1-6} alkoxyC_{1-6} alkyl, C_{3-7} cycloalkylC_{1-6} alkoxy, C_{1-6} alkanoyl, C_{1-6} alkoxycarbonyl, C_{1-6} alkylsulfonyl, C_{1-6} alkylsulfinyl, C_{1-6} alkylsulfonyloxy, C_{1-6} alkylsulfonylC_{1-6} alkyl, C_{1-6} alkylsulfonamidoC_{1-6} alkyl, C_{1-6} alkylamidoC_{1-6} alkyl or a group $NR^{15a}R^{16a}$, -$CONR^{15a}R^{16a}$, -$NR^{15a}COR^{16a}$, -$NR^{15a}SO_2R^{16a}$ or -$SO_2NR^{15a}R^{16a}$, wherein R^{15a} and R^{16a} independently represent hydrogen, C_{1-6} alkyl, aryl or together with the nitrogen to which they are attached may form a nitrogen containing heterocyclyl group;;

m is 1 or 2;

p is 0, 1, 2 or 3, or when p represents 2, said R^{4a} groups may instead form a bridging group consisting of one or two methylene groups;

or R^1 represents a group of formula (B):

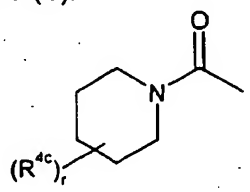


(B)

wherein $NR^{4b}R^{5b}$ represents an N-linked –heterocyclyl, -heterocyclyl-X^b-aryl, -heterocyclyl-X^b-heteroaryl, –heterocyclyl–X^b-heterocyclyl, -heteroaryl, -heteroaryl-X^b-aryl, -heteroaryl-X^b-heteroaryl or –heteroaryl-X^b-heterocyclyl group;

wherein said aryl, heteroaryl and heterocyclyl groups of $NR^{4b}R^{5b}$ may be optionally substituted by one or more substituents which may be the same or different, and which are selected from the group consisting of halogen, hydroxy, cyano, nitro, oxo, haloC_{1-6} alkyl, polyhaloC_{1-6} alkyl, haloC_{1-6} alkoxy, polyhaloC_{1-6} alkoxy, C_{1-6} alkyl, C_{1-6} alkoxy, arylC_{1-6} alkoxy, C_{1-6} alkylthio, C_{1-6} alkoxyC_{1-6} alkyl, C_{3-7} cycloalkylC_{1-6} alkoxy, C_{1-6} alkanoyl, C_{1-6} alkoxycarbonyl, arylC_{1-6} alkyl, heteroarylC_{1-6} alkyl, C_{1-6} alkylsulfonyl, C_{1-6} alkylsulfinyl, C_{1-6} alkylsulfonyloxy, C_{1-6} alkylsulfonylC_{1-6} alkyl, arylsulfonyl, arylsulfonyloxy, arylsulfonylC_{1-6} alkyl, aryloxy, C_{1-6} alkylsulfonamidoC_{1-6} alkyl, C_{1-6} alkylamidoC_{1-6} alkyl, arylsulfonamido, arylaminosulfonyl, arylsulfonamidoC_{1-6} alkyl, arylcarboxamidoC_{1-6} alkyl, aroylC_{1-6} alkyl, arylC_{1-6} alkanoyl, or a group $-NR^{15b}R^{16b}$, $-CONR^{15b}R^{16b}$, $-NR^{15b}COR^{16b}$, $-NR^{15b}SO_2R^{16b}$ or $-SO_2NR^{15b}R^{16b}$, wherein R^{15b} and R^{16b} independently represent hydrogen or C_{1-6} alkyl;
X^b represents a bond, CO, NHCO or CONH;

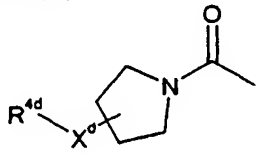
or R^1 represents a group of formula (C):



(C)

wherein R^{4c} represents C_{1-6} alkyl, OH, aryl or heterocyclyl, wherein said aryl and heterocyclyl groups may be optionally substituted by halogen, C_{1-6} alkyl, C_{1-6} alkoxy, cyano, amino, oxo, trifluoromethyl or an aryl group;
r is 0, 1 or 2;

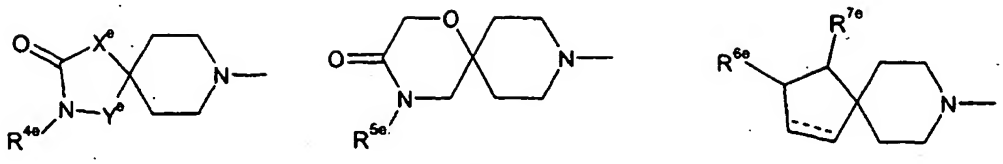
or R^1 represents a group of formula (D):



(D)

wherein R^{4d} represents aryl or heteroaryl wherein said aryl and heteroaryl groups may be optionally substituted by one or more substituents which may be the same or different, and which are selected from the group consisting of halogen, C_{1-6} alkyl, C_{1-6} alkoxy, cyano, amino or trifluoromethyl;
X^d represents a bond or NHCO, such that when X^d represents NHCO, the group R^{4d}-X^d is attached at the 3-position of the pyrrolidinyl ring;

or R^1 represents a group of formula –CO-E, wherein E represents a group of formula E^a, E^b or E^c:



(E^a) (E^b) (E^c)

wherein X^e represents O or N-R^{8e};

Y^e represents –C(HR^{9e})- or –C(=O)-;

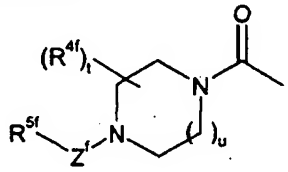
R^{4e}, R^{5e}, R^{8e} and R^{9e} independently represent hydrogen, C_{1-6} alkyl, aryl, heteroaryl, -C_{1-6} alkyl-aryl or -C_{1-6} alkyl-heteroaryl;

R^{6e} and R^{7e} independently represent hydrogen, C_{1-6} alkyl, aryl, heteroaryl, -C_{1-6} alkyl-aryl, -C_{1-6} alkyl-heteroaryl or R^{8e} and R^{7e} together with the carbon atoms to which they are attached may form a benzene ring;

⋯⋯ is a single or double bond;

wherein said aryl or heteroaryl groups of R^{4e}, R^{5e}, R^{8e}, R^{7e}, R^{8e} and R^{9e} may be optionally substituted by one or more substituents which may be the same or different, and which are selected from the group consisting of C_{1-6} alkyl, CF_3, C_{1-6} alkoxy, halogen, cyano, sulfonamide or C_{1-6} alkylsulfonyl;

or R^1 represents a group of formula (F):



(F)

wherein t is 0, 1 or 2;

u is 1 or 2;

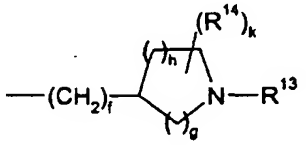
R^{4f} represents C_{1-6} alkyl or when t represents 2, said R^{4f} groups may instead form a bridging group consisting of one or two methylene groups;

R^{5f} represents -C_{1-6} alkyl, -C_{1-6} alkylC_{1-6} alkoxy, -C_{3-8} cycloalkyl, aryl, heterocyclyl, heteroaryl, -C_{1-6} alkyl-aryl, -C_{1-6} alkyl-C_{3-8} cycloalkyl, -C_{1-6} alkyl-heteroaryl, -C_{1-6} alkyl-heterocyclyl, -aryl-aryl, -aryl-heteroaryl, -aryl-heterocyclyl, -heteroaryl-aryl, -heteroaryl-heteroaryl, -heteroaryl-heterocyclyl, -heterocyclyl-aryl, -heterocyclyl-heteroaryl or -heterocyclyl-heterocyclyl;

wherein R^{5f} may be optionally substituted by one or more substituents which may be the same or different, and which are selected from the group consisting of halogen, hydroxy, cyano, nitro, oxo, haloC_{1-6} alkyl, polyhaloC_{1-6} alkyl, haloC_{1-6} alkoxy, polyhaloC_{1-6} alkoxy, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} alkylthio, C_{1-6} alkoxyC_{1-6} alkyl, C_{3-7} cycloalkylC_{1-6} alkoxy, C_{1-6} alkanoyl, C_{1-6} alkoxycarbonyl, C_{1-6} alkylsulfonyl, C_{1-6} alkylsulfinyl, C_{1-6} alkylsulfonyloxy, C_{1-6} alkylsulfonylC_{1-6} alkyl, C_{1-6} alkylsulfonamidoC_{1-6} alkyl, C_{1-6} alkylamidoC_{1-6} alkyl, arylsulfonyl, arylsulfonyloxy, aryloxy, arylsulfonamido, arylcarboxamido, aroyl, or a group $NR^{15f}R^{16f}$, -$CONR^{15f}R^{16f}$, -$NR^{15f}COR^{16f}$, -$NR^{15f}SO_2R^{16f}$ or -$SO_2NR^{15f}R^{16f}$, wherein R^{15f} and R^{16f} independently represent hydrogen or C_{1-6} alkyl or together form a heterocyclic ring;

Z^f represents CO or SO_2;

R^2 represents halogen, C_{1-6} alkyl, C_{1-6} alkoxy, cyano, amino or trifluoromethyl;
n is 0, 1 or 2;
R^3 represents $-(CH_2)_q-NR^{11}R^{12}$ or a group of formula (i):



(i)

wherein q is 2, 3 or 4;
R^{11} and R^{12} independently represent C_{1-6} alkyl or together with the nitrogen atom to which they are attached represent an N-linked heterocyclic group selected from pyrrolidine, piperidine and homopiperidine optionally substituted by one or two R^{17} groups;
R^{13} represents C_{1-6} alkyl, C_{3-6} cycloalkyl or $-C_{1-4}$ alkyl-C_{3-6} cycloalkyl;
R^{14} and R^{17} independently represent halogen, C_{1-6} alkyl, haloC_{1-6} alkyl, OH, diC_{1-6} alkylamino or C_{1-6} alkoxy;
f and k independently represent 0, 1 or 2;
g is 0, 1 or 2 and h is 0, 1, 2 or 3, such that g and h cannot both be 0;
or solvates thereof.

2. A compound according to claim 1 which is a compound of formula E1-E172 or a pharmaceutically acceptable salt thereof.

3. A pharmaceutical composition which comprises the compound of formula (I) as defined in claim 1 or claim 2 or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier or excipient.

4. A compound as defined in claim 1 or claim 2 for use in therapy.

5. A compound as defined in claim 1 or claim 2 for use in the treatment of neurological diseases.

6. Use of a compound as defined in claim 1 or claim 2 in the manufacture of a medicament for the treatment of neurological diseases.

7. A method of treatment of neurological diseases which comprises administering to a host in need thereof an effective amount of a compound of formula (I) as defined in claim 1 or claim 2 or a pharmaceutically acceptable salt thereof.

8. A pharmaceutical composition for use in the treatment of neurological diseases which comprises the compound of formula (I) as defined in claim 1 or claim 2 or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 03/11649

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D295/18 A61K31/496 A61P25/00 C07D295/22 C07D243/08
C07D213/74 C07D239/42 C07D239/46 C07D237/20 C07D215/46
C07D277/82 C07D241/08 C07D213/85 C07D487/08 C07D401/04

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, BEILSTEIN Data, CHEM ABS Data, BIOSIS, EMBASE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 02/076925 A (BEAVERS LISA SELSAM ;SCHAUS JOHN MEHNERT (US); WATSON BRIAN MORGAN) 3 October 2002 (2002-10-03) see claim 7, e.g. compound 155	1-8
Y	WO 02/12190 A (ORTHO MCNEIL PHARM INC) 14 February 2002 (2002-02-14) claim 1; example 76	1-8
A	WO 00/06254 A (SCHUNACK WALTER G ;SIGURD ELZ (DE); STARK HOLGER (DE); BIOPROJET S) 10 February 2000 (2000-02-10) claim 16	1-8

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
4 February 2004	18. 03. 2004

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx 31 651 epo nl, Fax: (+31-70) 340-3016	Steendijk, M

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

national application No.
PCT/EP 03/11649

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2 ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

1-8 (part)

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. claims: 1-8(part)

Compounds of formula (I) in which R1 represents groups (A) or (F) (carbonyl bound saturated N-linked heterocycle with two nitrogen atoms)

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2. claims: 1-8(part)

Compounds of formula (I) in which R1 represents group (B) (sulfonyl bound N-linked-heterocycle)

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3. claims: 1-8(part)

Compounds of formula (I) in which R1 represents groups (C) or (D) (carbonyl bound saturated N-linked heterocycle with one nitrogen atom)

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4. claims: 1-8(part)

Compounds of formula (I) in which R1 represents groups (E) (carbonyl bound spiro-fused N-linked heterocycle).

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/EP 03/11649

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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